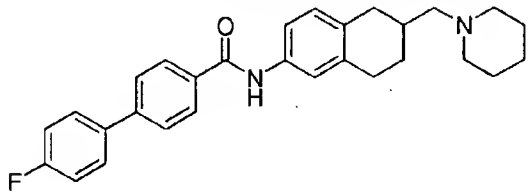
tetrahydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained by carrying out the same operation as in Example 1, using 6-(1-piperidinylmethyl)-5,6,7,8-tetrahydro-2-naphthalenamine obtained in Reference Example 53.

^{1}H NMR ($CDCl_3$) δ: 1.36-1.52 (8H, m), 2.29-2.31 (2H, m), 2.24-2.45 (6H, m), 2.82-2.93 (3H, m), 7.08-7.33 (4H, m), 7.44 (1H, s), 7.57-7.66 (4H, m), 7.74 (1H, s), 7.92 (2H, J = 8.1 Hz).

Elemental analysis for $C_{29}H_{31}FN_2O$

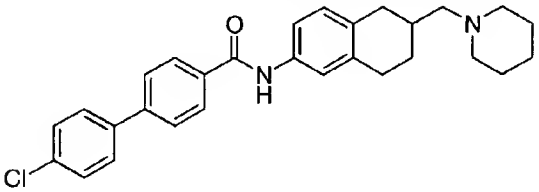
Calcd.: C, 78.70; H, 7.08; N, 6.33.

Found: C, 78.40; H, 7.09; N, 6.09.

Melting point: 179 - 181° C (crystallization solvent: ethyl acetate)

Example 55

4'-Chloro-N-[6-[1-piperidinylmethyl)-5,6,7,8-tetrahydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



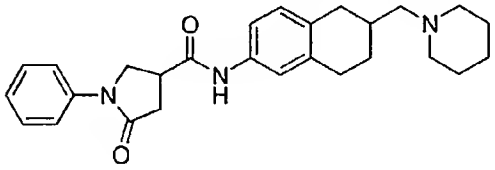
The titled compound was obtained by carrying out the same operation as in Example 1, using 6-(1-piperidinylmethyl)-5,6,7,8-tetrahydro-2-naphthalenamine obtained in Reference Example 53.

^{1}H NMR ($CDCl_3$) δ: 1.25-1.71 (8H, m), 1.95-2.00 (2H, m), 2.25-2.45 (6H, m), 2.83-2.93 (3H, m), 7.09 (1H, d, J = 8.3 Hz), 7.30-7.32 (1H, m), 7.43- 7.45 (3H, m), 7.55 (2H, d, J = 8.1 Hz), 7.65 (2H, d, J = 8.4 Hz), 7.77 (1H, s), 7.93 (2H, d, J = 8.1 Hz).

Melting point: 202 - 203°C (crystallization solvent: tetrahydrofuran - n-hexane)

Example 56

5-Oxo-1-phenyl-N-[6-(1-piperidinylmethyl)-5,6,7,8-tetrahydro-2-naphthalenyl]-3-pyrrolidinecarboxamide



The titled compound was obtained by carrying out the same operation as in Example 1, using 6-(1-piperidinylmethyl)-5,6,7,8-tetrahydro-2-naphthalenamine obtained in Reference Example 53.

^{1}H NMR ($CDCl_3$) δ: 1.03-3.33(22H, m), 3.97 (1H, t, J = 8.4 Hz), 4.21 (1H, dd, J = 6.8, 7.1 Hz), 6.91-7.63 (9H, m).

Elemental analysis for $C_{27}H_{33}N_3O_2$

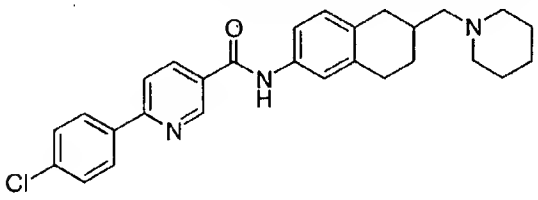
Calcd.: C, 75.14; H, 7.71; N, 9.74.

Found: C, 75.01; H, 7.33; N, 9.43.

Melting point: 162 - 164°C (crystallization solvent: ethyl acetate)

Example 57

6-(4-Chlorophenyl)-N-[6-(1-piperidinylmethyl)-5,6,7,8-tetrahydro-2-naphthalenyl]nicotinamide



The titled compound was obtained by carrying out the same operation as in Example 1, using 6-(1-piperidinylmethyl)-5,6,7,8-tetrahydro-2-naphthalenamine obtained in Reference Example 53.

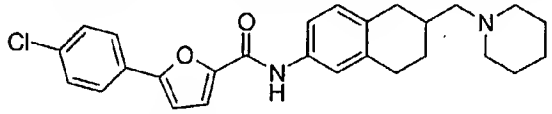
^{1}H NMR ($CDCl_3$) δ: 1.30-2.40 (16H, m), 2.82-2.92 (3H, m), 7.09 (1H, d, J = 8.1 Hz), 7.26-7.48 (4H, m), 7.80 (2H, d,

J = 8.7 Hz), 7.99 (2H, d, J = 8.7 Hz), 8.23 (d, 1H, J = 6.3 Hz), 9.11 (1H, s).

Melting point: 193 - 195° C (crystallization solvent: ethyl acetate)

Example 58

5-(4-Chlorophenyl)-N-[6-(1-piperidinylmethyl)-5,6,7,8-tetrahydro-2-naphthalenyl]-2-furamide

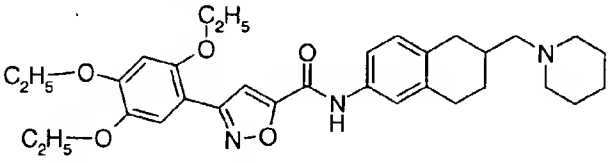


The titled compound was obtained by carrying out the same operation as in Example 1, using 6-(1-piperidinylmethyl)-5,6,7,8-tetrahydro-2-naphthalenamine obtained in Reference Example 53.

^{1}H NMR ($CDCl_3$) δ: 1.23-1.61 (7H, m), 1.96-2.00 (2H, m), 2.24-2.43 (7H, m), 2.80-2.92 (3H, m), 6.75 (1H, d, J = 3.6 Hz), 7.07 (1H, d, J = 8.4 Hz), 7.27 (1H, d, J = 3.6 Hz), 7.32-7.42 (4H, m), 7.66 (2H, d, J = 8.4 Hz), 8.32 (1H, s).

Example 59

N-[6-(1-Piperidinylmethyl)-5,6,7,8-tetrahydro-2-naphthalenyl]-3-(2,4,5-triethoxyphenyl)-5-isoxazolecarboxamide

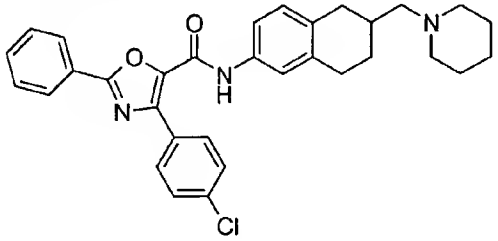


The titled compound was obtained by carrying out the same operation as in Example 1, using 6-(1-piperidinylmethyl)-5,6,7,8-tetrahydro-2-naphthalenamine obtained in Reference Example 53.

^{1}H NMR ($CDCl_3$) δ: 1.42-1.60 (18H, m), 1.97-2.36 (7H, m), 2.80-2.95 (3H, m), 4.06-4.18 (6H, m), 6.58 (1H, s), 7.09 (1H, d, J = 8.4 Hz), 7.35 (1H, d, J = 8.1 Hz), 7.44 (1H, s), 7.50 (1H, s), 7.55 (1H, s), 8.16 (1H, s).

Example 60

4-(4-Chlorophenyl)-2-phenyl-N-[6-(1-piperidinylmethyl)-5,6,7,8-tetrahydro-2-naphthalenyl]-1,3-oxazole-5-carboxamide

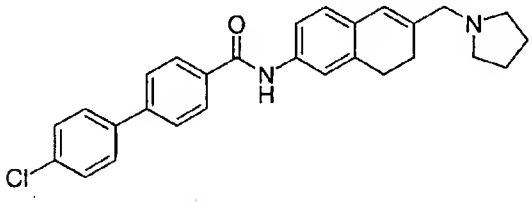


The titled compound was obtained by carrying out the same operation as in Example 1, using 6-(1-piperidinylmethyl)-5,6,7,8-tetrahydro-2-naphthalenamine obtained in Reference Example 53.

^{1}H NMR ($CDCl_3$) δ: 1.26-1.58 (7H, m), 1.90-2.00 (2H, m), 2.22-2.35 (7H, m), 2.70-2.95 (3H, m), 7.06 (1H, d, J = 8.1 Hz), 7.25-7.51 (7H, m), 8.04-8.32 (5H, m).

Example 61

4'-Chloro-N-[6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl][1,1-biphenyl]-4-carboxamide



The titled compound was obtained by carrying out the same operation as in Example 51, using 4'-chloro-N-[6-(chloromethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide obtained in Reference Example 56.

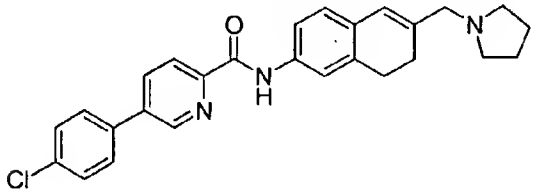
Melting point: 185 - 187°C (crystallization solvent: tetrahydrofuran - n-hexane)

^{1}H NMR ($CDCl_3$) δ: 1.83 (4H, s), 2.35 (2H, t, J = 8.1 Hz), 2.52 (4H, s), 2.84 (2H, t, J = 8.1 Hz), 3.18 (2H, s), 6.36 (1H, s), 7.02 (1H, d, J = 8.4 Hz), 7.39-7.56 (6H, m), 7.66

(2H, d, J = 7.5 Hz), 7.82 (1H, s), 7.93 (2H, d, J = 7.5 Hz).

Example 62

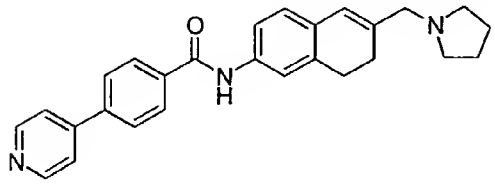
5-(4-Chlorophenyl)-N-[6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl]-2-pyridinecarboxamide



The titled compound was obtained by carrying out the same operation as in Example 51, using 4'-chloro-N-[6-(chloromethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide obtained in Reference Example 56.
^{1}H NMR ($CDCl_3$) δ: 1.80 (6H, s), 2.37 (2H, t, J = 8.1 Hz), 2.52 (4H, s), 2.87 (2H, t, J = 8.1 Hz), 3.18 (2H, s), 6.37 (1H, s), 7.03 (1H, d, J = 7.8 Hz), 7.48-7.61 (6H, m), 8.04 (1H, dd, J = 8.1, 2.1 Hz), 8.35 (1H, d, J = 8.1 Hz), 8.78 (1H, s), 9.95 (1H, s).

Example 63

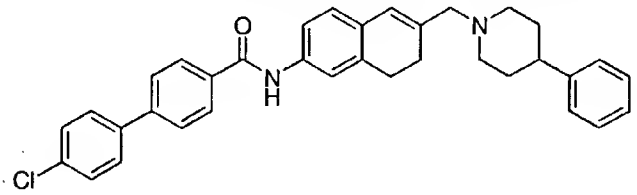
4-(4-Pyridinyl)-N-[6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl]benzamide



The titled compound was obtained by carrying out the same operation as in Example 1, using 6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 54.
^{1}H NMR ($CDCl_3$) δ: 1.79-1.83 (6H, m), 2.35 (2H,t, J = 8.1 Hz), 2.53 (4H, s), 2.73 (2H, t, J = 8.1 Hz), 3.18 (2H, s), 6.36 (1H, s), 7.02 (1H, d, J = 7.8 Hz), 7.38 (1H, d, J = 8.1 Hz), 7.48 (1H, s), 7.71-7.78 (4H, m), 7.89 (1H, s), 7.99 (1H, d, J = 8.4 Hz), 8.32 (2H, d, J = 8.4 Hz).

Example 64

4'-Chloro-N-[6-[(4-phenyl-1-piperidinyl)methyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



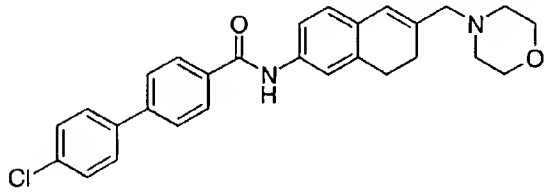
The titled compound was obtained by carrying out the same operation as in Example 51, using 4'-chloro-N-[6-(chloromethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide obtained in Reference Example 56.

^{1}H NMR ($CDCl_3$) δ: 1.83-2.10 (6H, m), 2.37 (2H, t, J = 8.1 Hz), 2.47-2.54 (1H, m), 2.86 (2H, t, J = 8.1 Hz), 3.03-3.10 (2H, m), 3.10 (2H, s), 6.37 (1H, s), 7.03 (1H, d, J = 8.4 Hz), 7.19-7.57 (11H, m), 7.66 (2H, d, J = 8.4 Hz), 7.81 (1H, s), 7.94 (2H, d, J = 8.4 Hz).

Melting point: 228 - 230°C (crystallization solvent: tetrahydrofuran - n-hexane)

Example 65

4'-Chloro-N-[6-(4-morpholinylmethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



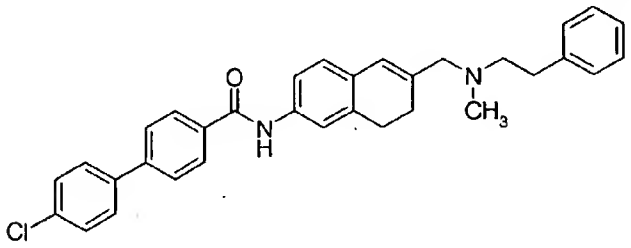
The titled compound was obtained by carrying out the same operation as in Example 51, using 4'-chloro-N-[6-(chloromethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide obtained in Reference Example 56.

^{1}H NMR ($CDCl_3$) δ: 2.34 (2H, t, J = 7.8 Hz), 2.45 (4H, s), 2.84 (2H, t, J = 7.8 Hz), 3.06 (2H, s), 3.73 (4H, s), 6.36 (1H, s), 7.02 (1H, d, J = 8.1 Hz), 7.36-7.57 (6H, m), 7.67 (2H, d, J = 8.4 Hz), 7.80 (1H, s), 7.94 (2H, d, J = 8.4 Hz).

Melting point: 194 - 195°C (crystallization solvent: tetrahydrofuran - n-hexane)

Example 66

4'-Chloro-N-(6-[[methyl(2-phenylethyl)amino]methyl]-7,8-dihydro-2-naphthalenyl[1,1'-biphenyl]-4-carboxamide

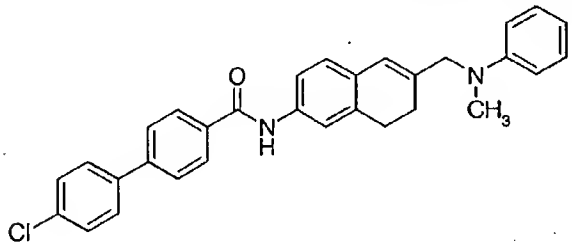


The titled compound was obtained by carrying out the same operation as in Example 51, using 4'-chloro-N-[6-(chloromethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide obtained in Reference Example 56. ^{1}H NMR ($CDCl_3$) δ : 2.25-2.32 (2H, m), 2.32 (3H, s), 2.60-2.66 (2H, m), 2.77-2.83 (4H, m), 3.10 (2H, s), 6.32 (1H, s), 6.93-7.95 (16H, m).

Melting point: 173 - 175°C (crystallization solvent: tetrahydrofuran - n-hexane)

Example 67

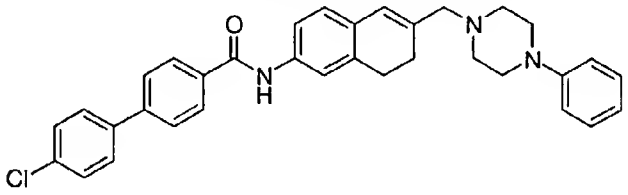
4'-Chloro-N-[6-[methylanilino)methyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained by carrying out the same operation as in Example 51, using 4'-chloro-N-[6-(chloromethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide obtained in Reference Example 56. ^{1}H NMR ($CDCl_3$) δ : 2.20-2.30 (2H, m), 2.25 (3H, s), 2.85-2.90

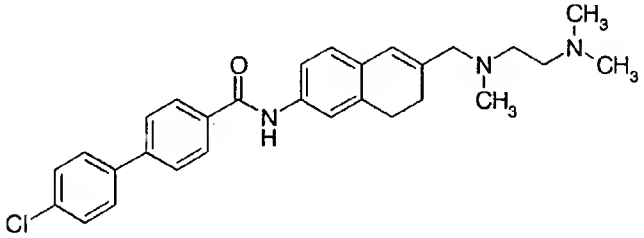
(2H, m), 3.00 (2H, s), 6.30 (1H, s), 6.74-7.95 (146H, m).
Melting point: 177 - 179°C (crystallization solvent: tetrahydrofuran - n-hexane)

Example 68
4'-Chloro-N-[6-[(4-phenyl-1-piperadinyl)methyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained by carrying out the same operation as in Example 51, using 4'-chloro-N-[6-(chloromethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide obtained in Reference Example 56.
^{1}H NMR ($CDCl_3$) δ: 2.37 (2H, t, J = 8.1 Hz), 2.62 (4h, S), 2.86 (2H, t, J = 8.4 Hz), 3.13 (2H, s), 3.22 (4H, s), 6.39 (1H, s), 6.85-7.95 (16H, m).
Melting point: 228 - 230°C (crystallization solvent: tetrahydrofuran - n-hexane)

Example 69
4'-Chloro-N-[6-[[[2-(dimethylamino)ethyl](methyl)amino]methyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



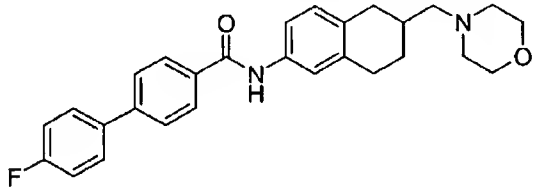
The titled compound was obtained by carrying out the same operation as in Example 51, using 4'-chloro-N-[6-(chloromethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide obtained in Reference Example 56.
^{1}H NMR ($CDCl_3$) δ: 2.25 (6H, s), 2.26 (3H, s), 2.33 (2H, t,

J = 8.1 Hz), 2.44-2.50 (4H, m), 2.84 (2H, t, J = 8.1 Hz), 3.07 (2H, s), 6.35 (1H, s), 7.02 (1H, d, J = 8.4 Hz), 7.37-7.57 (6H, m), 7.67 (2H, d, J = 8.1 Hz), 7.80 (1H, s), 7.94 (2H, d, J = 8.4 Hz).

Melting point: 156 - 158°C (crystallization solvent: tetrahydrofuran - n-hexane)

Example 70

4'-Fluoro-N-[6-(4-morpholinylmethyl)-5,6,7,8-tetrahydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



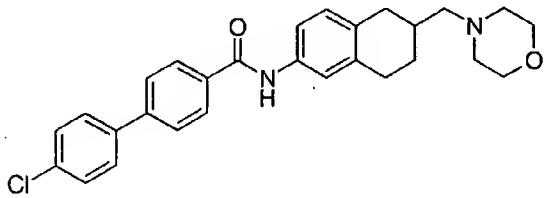
The titled compound was obtained by carrying out the same operation as in Example 1, using 6-(4-morpholinylmethyl)-5,6,7,8-tetrahydro-2-naphthalenamine obtained in Reference Example 57.

^{1}H NMR ($CDCl_3$) δ: 1.40-1.50 (1H, m), 1.90-2.10 (2H, m), 2.29-2.45 (7H, m), 2.80-2.92 (3H, m), 3.72-3.75 (4H, m), 7.07-7.33 (4H, m), 7.46 (1H, s), 7.56-7.66 (4H, m), 7.78 (1H, s), 7.92 (2H, d, J = 8.1 Hz).

Melting point: 188 - 190°C (crystallization solvent: ethyl acetate)

Example 71

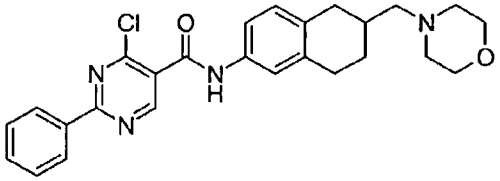
4'-Chloro-N-[6-(4-morpholinylmethyl)-5,6,7,8-tetrahydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained by carrying out the same operation as in Example 1, using 6-(4-morpholinylmethyl)-5,6,7,8-tetrahydro-2-naphthalenamine

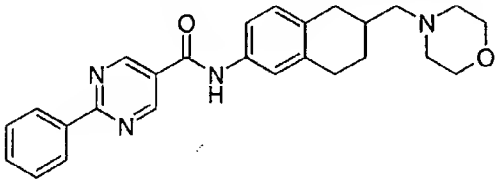
obtained in Reference Example 57.
^{1}H NMR ($CDCl_3$) δ: 1.40-1.50 (1H, m), 1.90-2.10 (2H, m), 2.32-2.45 (7H, m), 2.80-2.90 (3H, m), 3.70-3.80 (4H, m), 7.10-7.92 (12H, m).
Melting point: 216 - 218° C (crystallization solvent: ethyl acetate)

Example 72
4-Chloro-N-[6-(4-morpholinylmethyl)-5,6,7,8-tetrahydro-2-naphthalenyl]-2-phenyl-5-pyrimidinecarboxamide



The titled compound was obtained by carrying out the same operation as in Example 1, using 6-(4-morpholinylmethyl)-5,6,7,8-tetrahydro-2-naphthalenamine obtained in Reference Example 57.
^{1}H NMR ($CDCl_3$) δ: 1.40-1.50 (1H, m), 1.95-2.05 (2H, m), 2.29-2.45 (7H, m), 2.80-2.95 (3H, m), 3.73 (4H, t, J = 4.5 Hz), 7.10 (1H, d, J = 8.1 Hz), 7.32 (1H, d, J = 8.1 Hz), 7.42 (1H, s), 7.49-7.56 (3H, m), 8.25 (1H, s), 8.48 (2H, d, J = 6.6 Hz), 9.20 (1H, s)

Example 73
N-[6-(4-Morpholinylmethyl)-5,6,7,8-tetrahydro-2-naphthalenyl]-2-phenyl-5-pyrimidinecarboxamide



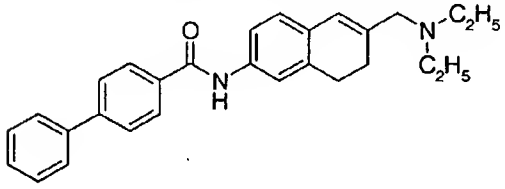
The titled compound was obtained by carrying out the same operation as in Reference Example 48, using 4-chloro-N-[6-(4-morpholinylmethyl)-5,6,7,8-tetrahydro-2-naphthalyl]-2-phenyl-5-pyrimidinecarboxamide obtained in

Example 72.

^{1}H NMR ($CDCl_3$) δ: 1.21-1.30 (1H, m), 1.93-2.03 (2H, m), 2.28 -2.44 (7H, m), 2.80-2.90 (3H, m), 3.73 (4H, t, J = 4.8 Hz), 7.07 (1H, d, J = 8.1 Hz), 7.26 -7.30 (1H, m), 7.39 (1H, s), 7.51-7.53 (3H, m), 8.00 (1H, s), 8.50 (2H, dd, J = 8.1, 2.4 Hz), 9.21 (2H, s)

Example 74

N-[6-[(Diethylamino)methyl]-7,8-dihydro-2-naphthalenyl] [1,1'-biphenyl]-4-carboxamide



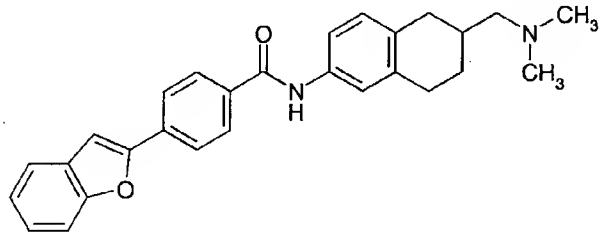
The titled compound was obtained by carrying out the same operation as in Example 51, using N-[6-(chloromethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide obtained in Reference Example 58.

^{1}H NMR ($CDCl_3$) δ: 1.24 (6H, t, J = 7.2 Hz), 2.33 (2H, t, J = 5.1 Hz), 2.53 (4H, q, J = 7.2 Hz), 2.84 (2H, t, J = 5.1 Hz), 3.11 (2H, s), 6.36 (1H, s), 7.02 (1H, d, J = 8.1 Hz), 7.37-7.50 (5H, m), 7.63 (2H, d, J = 8.7 Hz), 7.71 (2H, d, J = 8.4 Hz), 7.79 (1H, s), 7.93 (2H, d, J = 8.4 Hz).

Melting point: 153 - 155°C (crystallization solvent: tetrahydrofuran - n-hexane)

Example 75

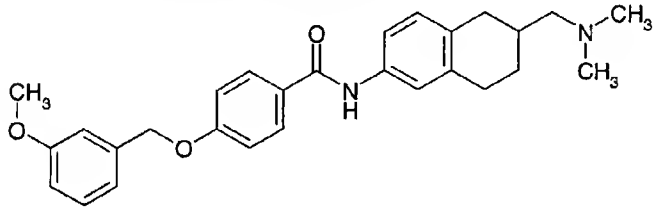
4-(2-Benzo[b]furanyl)-N-[2-(N,N-dimethylamino)methyl-6-tetralinyl]benzamide



The titled compound was obtained by carrying out the

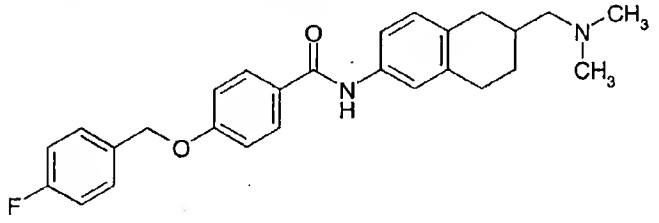
same operation as in Example 4, using 6-amino-2-[(N,N-dimethylamino)methyl]tetralin hydrochloride.
Melting point: 192 - 194°C (crystallization solvent: tetrahydrofuran-isopropyl ether)

Example 76
4-(3-Methoxybenzyloxy)-N-[2-(N,N-dimethylamino)methyl-6-tetralinyl]benzamide



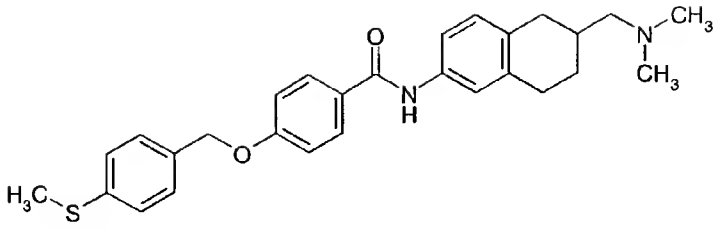
The titled compound was obtained by carrying out the same operation as in Example 4, using 6-amino-2-[(N,N-dimethylamino)methyl]tetralin hydrochloride.
Melting point: 102 - 104°C (crystallization solvent: isopropyl ether)

Example 77
4-(4-Fluorobenzyloxy)-N-[2-(N,N-dimethylamino)methy-6-tetralinyl]benzamide



The titled compound was obtained by carrying out the same operation as in Example 4, using 6-amino-2-[(N,N-dimethylamino)methyl]tetralin hydrochloride.
Melting point: 165 - 167°C (crystallization solvent: tetrahydrofuran-hexane)

Example 78
4-[4-(Methylsulfanyl)benzyloxy]-N-[2-(N,N-dimethylamino)methyl-6-tetralinyl]benzamide

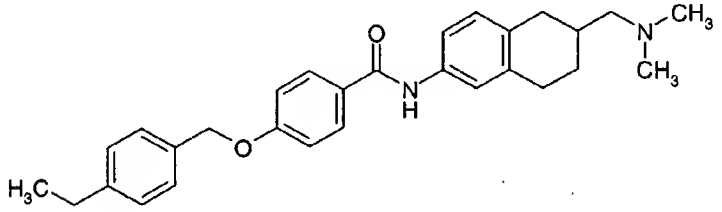


The titled compound was obtained by carrying out the same operation as in Example 4, using 6-amino-2-[(N,N-dimethylamino)methyl]tetralin hydrochloride.

Melting point: 162 - 163°C (crystallization solvent: tetrahydrofuran-hexane)

Example 79

4-(4-Ethylbenzyloxy)-N-[2-(N,N-dimethylamino)methyl-6-tetralinyl]benzamide

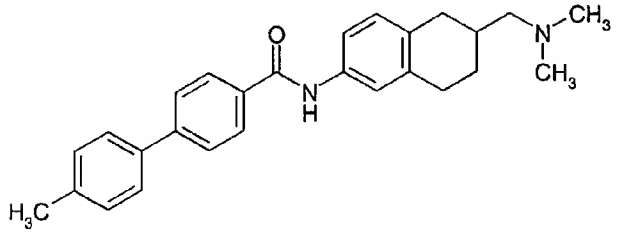


The titled compound was obtained by carrying out the same operation as in Example 4, using 6-amino-2-[(N,N-dimethylamino)methyl]tetralin hydrochloride.

Melting point: 120 - 122°C (crystallization solvent: tetrahydrofuran-isopropyl ether)

Example 80

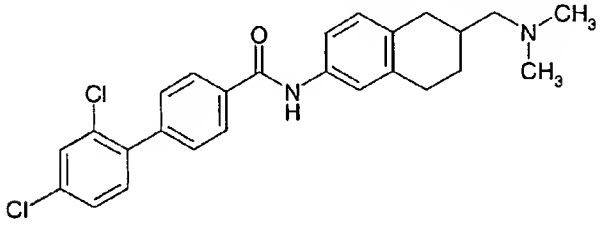
(4'-Methylbiphenyl-4-yl)-N-[2-(N,N-dimethylamino)methyl-6-tetralinyl]carboxamide



The titled compound was obtained by carrying out the same operation as in Example 4, using 6-amino-2-[(N,N-

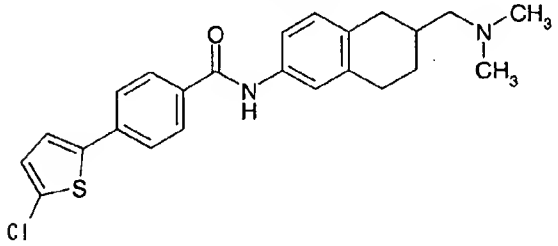
dimethylamino)methyl]tetralin hydrochloride.
Melting point: 181 - 182° C (crystallization solvent: ethyl acetate-hexane)

Example 81
(2',4'-Dichlorobiphenyl-4-yl)-N-[2-(N,N-dimethylamino)methyl-6-tetralinyl]carboxamide



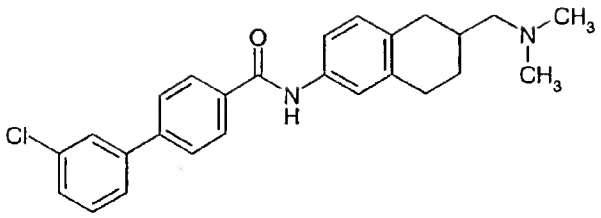
The titled compound was obtained by carrying out the same operation as in Example 4, using 6-amino-2-[(N,N-dimethylamino)methyl]tetralin hydrochloride.
Melting point: 188 - 189° C (crystallization solvent: tetrahydrofuran-hexane)

Example 82
4-(5-Chloro-2-thienyl-N-[2-(N,N-dimethylamino)methyl-6-tetralinyl]benzamide



The titled compound was obtained by carrying out the same operation as in Example 4, using 6-amino-2-(N,N-dimethylamino)methyltetraline hydrochloride.
Melting point: 167 - 169° C (crystallization solvent: ethyl acetate-hexane)

Example 83
(3'-Chlorobiphenyl-4-yl)-N-[2-(N,N-dimethylamino)methyl-6-tetralinyl]carboxamide

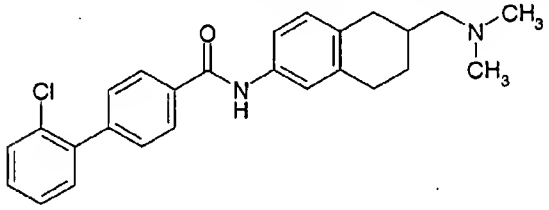


The titled compound was obtained by carrying out the same operation as in Example 4, using 6-amino-2-[(N,N-dimethylamino)methyl]tetralin hydrochloride.

Melting point: 138 - 139°C (crystallization solvent: tetrahydrofuran-isopropyl ether)

Example 84

(2'-Chlorobiphenyl-4-yl)-N-[2-(N,N-dimethylamino)methyl-6-tetralinyl]carboxamide

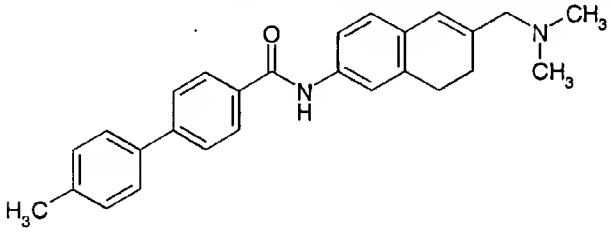


The titled compound was obtained by carrying out the same operation as in Example 4, using 6-amino-2-[(N,N-dimethylamino)methyl]tetralin hydrochloride.

Melting point: 176 - 177°C (crystallization solvent: tetrahydrofuran-hexane)

Example 85

4'-Methyl-N-[6-[N,N-dimethylamino)methyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained by carrying out the same operation as in Example 1, using 6-[(N,N-dimethylamino)methyl]-7,8-dihydro-2-naphthalenamine

obtained in Example 41-2).

^{1}H-NMR ($CDCl_3$) δ: 2.25 (6H,s), 2.33 (2H, t, J = 8.1 Hz), 2.41 (3H, s), 2.84 (2H, t, J = 8.1 Hz), 2.98 (2H, s), 6.33 (1H, s), 7.01 (1H, d, J = 7.8 Hz), 7.39 (1H, d, J = 8.4 Hz), 7.48 (1H, s), 7.52 (2H, d, J = 7.8 Hz), 7.67 (2H, d, J = 8.1 Hz), 7.84 (1H, s), 7.91 (2H, d, J = 8.1 Hz).

Elemental analysis for $C_{27}H_{28}N_2O$

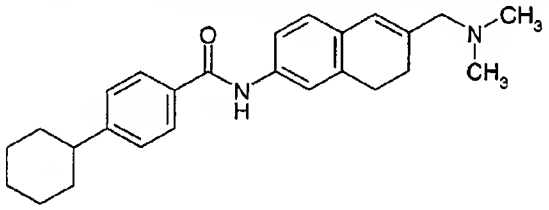
Calcd.: C, 81.78; H, 7.12; N, 7.06

Found: C, 81.51; H, 7.22; N, 6.93

Melting point: 195 - 196°C (crystallization solvent: ethyl acetate-diisopropyl ether)

Example 86

4-Cyclohexyl-N-[6-[(N,N-dimethylamino)methyl]-7,8-dihydro-2-naphthalenyl]benzamide



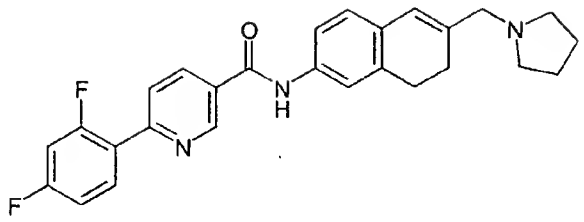
The titled compound was obtained by carrying out the same operation as in Example 1, using the 6-[(N,N-dimethylamino)methyl]-7,8-dihydro-2-naphthalenamine obtained in Example 41-2).

^{1}H-NMR ($CDCl_3$) δ: 1.20-1.52 (4H,m), 1.71-1.96 (6H, m), 2.25 (6H, s), 2.33 (2H, t, J = 8.1 Hz), 2.50-2.62 (1H, m), 2.84 (2H, t, J = 8.1 Hz), 2.99 (2H, s), 6.33 (1H, s), 7.00 (1H, d, J = 7.8 Hz), 7.31 (2H, d, J = 8.1 Hz), 7.36 (1H, d, J = 7.8 Hz), 7.46 (1H, brs), 7.75 (1H, s), 7.78 (2H, d, J = 8.1 Hz).

Melting point: 179 - 181°C (crystallization solvent: ethyl acetate-diisopropyl ether)

Example 87

6-(2,4-Difluorophenyl)-N-[6-[(1-pyrrolidinyl)methyl]-7,8-dihydro-2-naphthalenyl]nicotinamide



The titled compound was obtained by carrying out the same operation as in Example 1, using 6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 54.

^{1}H-NMR ($CDCl_3$) δ: 1.81 (4H, m), 2.37 (2H, t, J = 8.1 Hz), 2.54 (4H, m), 2.86 (2H, t, J = 8.1 Hz), 3.18 (2H, s), 6.37 (1H, s), 6.93 (1H, m), 7.04 (2H, m), 7.38 (1H, m), 7.47 (1H, s), 7.77 (1H, s), 7.91 (1H, m), 8.13 (1H, m), 8.24 (1H, m), 9.16 (1H, s).

Elemental analysis for $C_{27}H_{26}F_2N_3O$

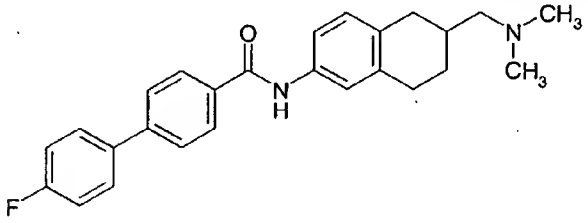
Calcd.: C, 72.79; H, 5.66; N, 9.43

Found: C, 72.65; H, 5.52; N, 9.73

Melting point: 169 - 170°C (crystallization solvent: ethyl acetate - diisopropyl ether)

Example 88

4'-Fluoro-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained by carrying out the same operation as in Example 4, using 6-amino-2-[(N,N-dimethylamino)methyl]tetralin hydrochloride.

^{1}H-NMR ($CDCl_3$) δ: 1.41 (1H, m), 1.95 (2H, m), 2.25-2.45 (3H, m), 2.36 (6H, s), 2.85-2.94 (3H, m), 7.13 (3H, m), 7.30 (1H, m), 7.46 (1H, s), 7.59 (2H, m), 7.65 (2H, d, J = 8.1 Hz), 7.74 (1H, s), 7.93 (2H, d, J = 8.1 Hz).

Elemental analysis for $C_{26}H_{27}FN_2O$

Calcd. : C, 77.58; H, 6.76; N, 6.96
Found : C, 77.72; H, 6.49; N, 6.79
Melting point: 184 - 186° C (crystallization solvent: ethyl acetate - diisopropyl ether)

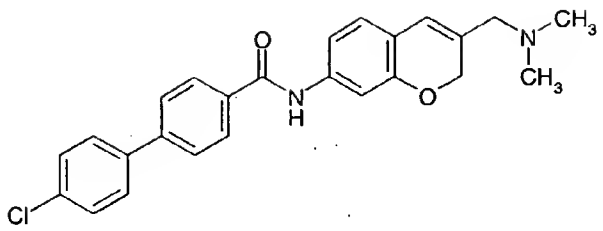
Example 89
(+)-4'-Fluoro-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide, and (-)-4'-fluoro-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide

Optical resolution of 4'-fluoro-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide (2.00 g) obtained in Example 88 was conducted by sample-splitting HPLC using a chiral column (Daicel Co., CHIRALCEL OD 500 mmD × 500 mmL; moving phase n-hexane:ethanol = 85:15), to give (+) form (1.00 g; 99.8%ee) and (-) form (0.89 g; >99.9%ee) as powders. The powders obtained were respectively recrystallized using ethyl acetate - diispropyl ether, to give the (+) form (855 mg) and (-) form (754 mg) of the titled compounds. The optical rotation of both compounds are shown below.

(+)-4'-fluoro-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide
Optical rotation: $[\alpha]_D$ = +50.8° C=0.494% (methanol)

(-)-4'-fluoro-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide
Optical rotation: $[\alpha]_D$ = +51.2° C=0 .492% (methanol)

Example 90
4'-Chloro-N-[3-[(N,N-dimethylamino)methyl]-2H-chromen-7-yl][1,1'-biphenyl]-4-carboxamide



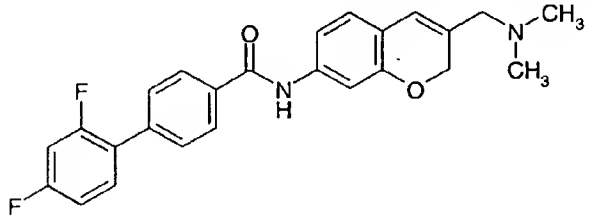
The titled compound was obtained by carrying out the same operation as in Example 1, using 3-[(N,N-dimethylamino)methyl]-2H-chromen-7-amine obtained in Reference Example 59.

^{1}H-NMR ($CDCl_3$) δ : 2.23 (6H, s), 2.97 (2H, s), 4.79 (2H, s), 6.30 (1H, s), 6.96 (1H, d, J = 8.1 Hz), 7.13 (1H, s), 7.20 (1H, d, J = 8.1 Hz), 7.45 (2H, d, J = 8.6 Hz), 7.56 (2H, d, J = 8.6 Hz), 7.66 (2H, d, J = 8.4 Hz), 7.74 (1H, brs), 7.93 (2H, d, J = 8.4 Hz).

Melting point: 199 - 208°C (crystallization solvent: diisopropyl ether)

Example 91

2',4'-Difluoro-N-[3-[N,N-dimethylamino)methyl]-2H-chromen-7-yl][1,1'-biphenyl]-4-carboxamide



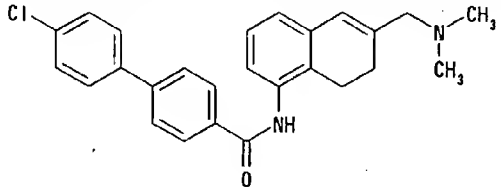
The titled compound was obtained by carrying out the same operation as in Example 1, using 3-[(N,N-dimethylamino)methyl]-2H-chromen-7-amine obtained in Reference Example 59.

^{1}H-NMR ($CDCl_3$) δ : 2.23 (6H, s), 2.97 (2H, s), 4.78 (2H, s), 6.29 (1H, s), 6.80-7.10 (2H, m), 6.96 (1H, d, J = 8.1 Hz), 7.13 (1H, s), 7.20 (1H, d, J = 8.1 Hz), 7.40-7.50 (1H, m), 7.62 (2H, d, J = 8.4 Hz), 7.76 (1H, brs), 7.92 (2H, d, J = 8.4 Hz).

Melting point: 200 - 204°C (crystallization solvent: diisopropyl ether)

Example 92

4'-Chloro-N-[6-[(dimethylamino)methyl]-7,8-dihydro-1-naphthalenyl][1,1'-biphenyl]-4-carboxamide



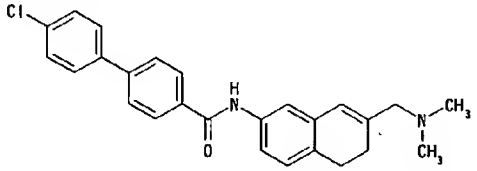
The titled compound was obtained in the same manner as in Example 1, using 6-[(dimethylamino)methyl]-7,8-dihydro-1-naphthalenamine obtained in Reference Example 60.

^{1}H-NMR ($CDCl_3$) δ : 2.34 (6H, s), 2.36 (2H, t, J=8.1 Hz), 2.80 (2H, t, J=8.1 Hz), 3.00 (2H, s), 6.38 (1H, s), 6.94 (1H, d, J=7.8 Hz), 7.21 (1H, t, J=7.8 Hz), 7.45 (2H, d, J=8.6 Hz), 7.56 (2H, d, J=8.6 Hz), 7.61 (2H, m), 7.68 (2H, d, J=8.4 Hz), 7.97 (2H, d, J=8.4 Hz).

Melting point: 193 - 195°C (crystallization solvent : diisopropyl ether)

Example 93

4'-Chloro-N-[7-[(dimethylamino)methyl]-5,6-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide

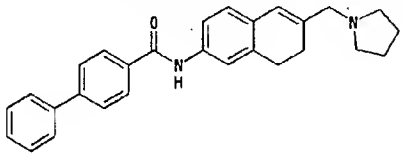


The titled compound was obtained as a white powder by the same method as in Example 1, using 7-[(dimethylamino)methyl]-5,6-dihydro-2-naphthalenamine obtained in Reference Example 61.

^{1}H-NMR ($CDCl_3$) δ : 2.25 (6H, s), 2.34 (2H, t, J=8.1 Hz), 2.82 (2H, t, J=8.1 Hz), 3.00 (2H, s), 6.36 (1H, s), 7.11 (1H, d, J=7.5 Hz), 7.34 (1H, d, J=8.1 Hz), 7.38 (1H, s), 7.44

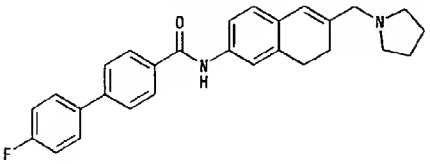
(2H, d, J=8.4 Hz), 7.56 (2H, d, J=8.4 Hz), 7.66 (2H, d, J=8.4 Hz), 7.78 (1H, brs), 7.97(2H, d, J=8.4 Hz).
Melting point: 167 - 169°C (crystallization solvent : diisopropyl ether)

Example 94
N-[6-(1-Pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained as a white powder in the same manner as in Example 1, using 6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 54.
^{1}H-NMR ($CDCl_3$) δ : 1.75-1.90 (4H, m), 2.34 (2H, t, J=8.1 Hz), 2.45-2.60 (4H, m), 2.85 (2H, t, J=8.1 Hz), 3.18 (2H, s), 6.36 (1H, s), 7.02 (1H, d, J=8.1 Hz), 7.27-7.55 (5H, m), 7.63 (2H, d, J=7.3 Hz), 7.70 (2H, d, J=8.4 Hz), 7.82 (1H, s), 7.94 (2H, d, J=8.1 Hz).
Elemental analysis for $C_{28}H_{28}N_2O$
Calcd. : C, 82.32; H, 6.91; N, 6.86.
Found : C, 81.99; H, 6.69; N, 6.91.
Melting point: 176 - 177°C (crystallization solvent : diisopropyl ether)

Example 95
4'-Fluoro-N-[6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained in the same manner as in Example 1, using 6-(1-pyrrolidinylmethyl)-7,8-

dihydro-2-naphthalenamine obtained in Reference Example 54.

^{1}H-NMR ($CDCl_3$) δ : 1.75-1.90 (4H, m), 2.35 (2H, t, J=8.2 Hz), 2.45-2.60 (4H, m), 2.84 (2H, t, J=8.2 Hz), 3.18 (2H, s), 6.36 (1H, s), 7.01(1H, d, J=8.1 Hz), 7.16 (2H, t, J=8.1 Hz), 7.38 (1H, d, J=8.1 Hz), 7.48 (1H, brs), 7.56-7.61 (2H, m), 7.64 (2H, d, J=8.4 Hz), 7.83 (1H, s), 7.93 (2H, d, J=8.4 Hz).

Elemental analysis for $C_{28}H_{27}FN_2O$

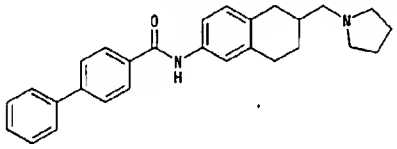
Calcd. : C, 78.85; H, 6.38; N, 6.57.

Found : C, 78.75; H, 6.39; N, 6.45.

Melting point: 189 - 192°C (crystallization solvent : diisopropyl ether)

Example 96

N-[6-(1-Pyrrolidinylmethyl)-5,6,7,8-tetrahydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained as a white powder in the same manner as in Example 1, using 6-(1-pyrrolidinylmethyl)-5,6,7,8-tetrahydro-2-naphthalenamine obtained in Reference Example 55.

^{1}H-NMR ($CDCl_3$) δ : 1.40-1.50 (1H, m), 1.80 (4H, m), 1.80-2.10 (1H, m), 1.80-2.20 (8H, m), 3.30-4.00 (3H, m), 7.29 (1H, d, J=8.4 Hz), 7.25-7.30 (1H, m), 7.30-7.55 (4H, m), 6.43 (2H, d, J=7.0 Hz), 7.70 (2H, t, J=8.4 Hz), 7.75 (1H, s), 7.94 (2H, d, J=8.4 Hz).

Elemental analysis for $C_{28}H_{30}N_2O$

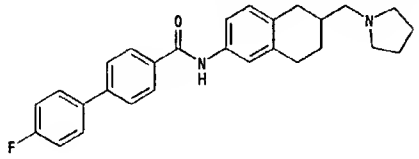
Calcd. : C, 81.91; H, 7.37; N, 6.82.

Found : C, 81.53; H, 7.25; N, 6.86.

Melting point: 144 - 146°C (crystallization solvent : diisopropyl ether)

Example 97

4'-Fluoro-N-[6-(1-pyrrolidinylmethyl)-5,6,7,8-tetrahydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained as a white powder in the same manner as in Example 1, using 6-(1-pyrrolidinylmethyl)-5,6,7,8-tetrahydro-2-naphthalenamine obtained in Reference Example 55.

^{1}H-NMR ($CDCl_3$) δ : 1.40-1.50 (1H, m), 1.80 (4H, m), 1.80-2.10 (1H, m), 1.80-2.20 (8H, m), 3.30-4.00 (3H, m), 7.08 (1H, d, J=8.1 Hz), 7.15 (2H, t, J=8.4 Hz), 7.30 (1H, d, J=8.1 Hz), 7.44 (1H, brs), 7.56-7.61 (2H, m), 7.62 (2H, d, J=8.1 Hz), 7.85 (1H, s), 7.92 (2H, d, J=8.1 Hz).

Elemental analysis for $C_{28}H_{29}FN_2O$

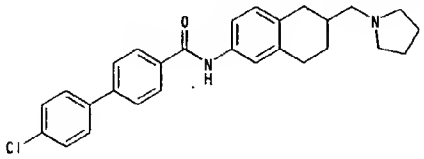
Calcd. : C, 78.48; H, 6.82; N, 6.54.

Found : C, 78.18; H, 6.60; N, 6.60.

Melting point: 185 - 189°C (crystallization solvent : diisopropyl ether)

Example 98

4'-Chloro-N-[6-(1-pyrrolidinylmethyl)-5,6,7,8-tetrahydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide

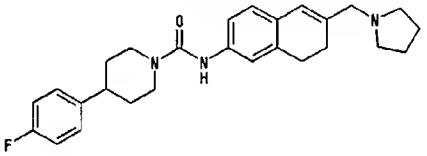


The titled compound was obtained as a white powder in the same manner as in Example 1, using 6-(1-pyrrolidinylmethyl)-5,6,7,8-tetrahydro-2-naphthalenamine obtained in Reference Example 55.

^{1}H-NMR ($CDCl_3$) δ : 1.40-1.50 (1H, m), 1.80 (4H, m), 1.80-2.10 (1H, m), 1.80-2.20 (8H, m), 3.30-4.00 (3H, m), 7.08 (1H, d, J=8.1 Hz), 7.31 (1H, d, J=8.4 Hz), 7.43 (2H, d, J=8.7 Hz), 7.45 (1H, s), 7.54 (2H, d, J=8.7 Hz), 7.64 (2H, d, J=8.4

Hz), 7.80 (1H, s), 7.93 (2H, d, J=8.4 Hz).
Elemental analysis for $C_{28}H_{29}ClN_2O$
Calcd.: C, 75.57; H, 6.57; N, 6.30.
Found: C, 75.26; H, 6.68; N, 6.15.
Melting point: 206 - 209°C (crystallization solvent : diisopropyl ether)

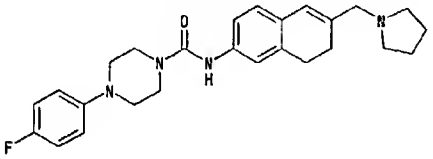
Example 99
4-(4-Fluorophenyl)-N-[6-(1-piperidinylmethyl)-7,8-dihydro-2-naphthalenyl]-1-piperidinecarboxamide



6-(1-Pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 54 (50 mg, 0.22 mmol) and pyridine (35 mg, 0.44 mmol) were dissolved in tetrahydrofuran (3 ml). Phenyl chlorocarbonate (38 mg, 0.24 mol) was added to the solution under ice-cooling, which was stirred for 10 minutes. The reaction mixture was concentrated, and dimehtylsulfoxide (5 ml) was added to the residue. 4-(4-Fluorophenyl)piperidine hydrochloride (57 mg, 0.26 mmol) and 4N aqueous sodium hydroxide solution (0.066 ml, 0.26 mmol) were added to the reaction mixture at room temperature while stirring, which was stirred for 30 minutes. Ethyl acetate and water were added to the mixture, and extraction was conducted. The organic layer was washed with water, and concentrated. Diisopropyl ether was added to the residue. The crystallized product was collected by filtration, washed with diisopropyl ether, to give 4-(4-fluorophenyl)-N-[6-(1-piperidinylmethyl)-7,8-dihydro-2-naphthalenyl]-1-piperidinecarboxamide (48 mg) as a white powder.
^{1}H-NMR ($CDCl_3$) δ: 1.60-1.70 (2H, m), 1.79 (4H, m), 1.80-1.90 (2H, m), 2.33 (2H, t, J=7.8 Hz), 2.51 (4H, m), 2.60-2.70 (1H, m), 2.80 (2H, t, J=7.8 Hz), 2.90-3.10 (2H, m), 3.16

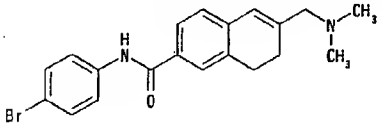
(2H, s), 4.18-4.23 (2H, m), 6.32 (1H, s), 6.32 (1H, s), 6.92-7.09 (4H, m), 7.15-7.20 (3H, m).
Melting point: 182 - 185°C (crystallization solvent : diisopropyl ether)

Example 100
4-(4-Fluorophenyl)-N-[6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl]-1-piperazinecarboxamide



The titled compound was obtained as a white powder in the same manner as in Example 99, using 6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 54 and 4-fluorophenylpiperazine.
^{1}H-NMR ($CDCl_3$) δ: 1.79 (4H, m), 2.32 (2H, t, J=7.8 Hz), 2.51(4H, m), 2.80 (2H, t, J=7.8 Hz), 3.13-3.16 (4H, m), 3.16 (2H, s), 3.63-3.66 (4H, m), 6.30 (1H, s), 6.32 (1H, s), 6.88-7.08 (6H, m), 7.19 (1H, s).
Elemental analysis for $C_{26}H_{31}FN_4O$
Calcd.: C, 71.86; H, 7.19; N, 12.89.
Found: C, 71.68; H, 7.35; N, 12.65.
Melting point: 179 - 181°C (crystallization solvent : diisopropyl ether)

Example 101
N-(4-Bromophenyl)-6-[(dimethylamino)methyl]-7,8-dihydro-2-naphthalenecarboxamide



1) 6-Cyano-1-tetralone (1.30 g, 7.59 mmol) synthesized by a known method by documents (synthetic communications, 23(21), 2965 (1993)) was dissolved in a

mixed solution of concentrated hydrochloric acid (10 ml) and acetic acid (20 ml), which was stirred at 120℃ for 16 hours. The reaction mixture was concentrated. Ethyl acetate and water were added to the residue, and extraction was conducted. The organic layer was washed with water, and concentrated. The residue was washed with ethyl acetate - n-hexane (1:1), to give 5-oxo-5,6,7,8-tetrahydro-2-naphthalenecarboxylic acid (1.10 g) as a white powder.

^{1}H-NMR ($CDCl_3$) δ: 2.15-2.23 (2H, m), 2.70-2.75 (2H, m), 3.04-3.07 (2H, m), 8.01-8.03 (1H, m), 8.03 (1H, s), 8.13 (1H, d, J=8.7 Hz).

2) N-(4-Bromophenyl)-5-oxo-5,6,7,8-tetrahydro-2-naphthalenecarboxamide (1.21 g) was obtained as a white powder in the same manner as in Example 1, using 5-oxo-5,6,7,8-tetrahydro-2-naphthalenecarboxylic acid (1.00 g, 5.26 mmol) obtained in 1) and 4-bromoaniline (0.90 g, 5.26 mmol).

^{1}H-NMR ($CDCl_3$) δ: 2.14-2.23 (2H, m), 2.69-2.73 (2H, m), 3.03-3.07 (2H, m), 7.48-7.58 (4H, m), 7.71 (1H, d, J=8.1 Hz), 7.79(1H, s), 7.86 (1H, s), 8.12 (1H, d, J=8.1 Hz).

3) N-(4-Bromophenyl)-5-oxo-5,6,7,8-tetrahydro-2-naphthalenecarboxamide (1.10 g, 3.19 mmol) obtained in 2) was dissolved in dimethylformamide diethylacetal (30 ml), which was refluxed with heating for 4 hours. The crystallized product was collected by filtration, washed with ethyl acetate, to give N-(4-bromophenyl)-6-[(dimethylamino)methylidene]-5-oxo-5,6,7,8-tetrahydro-2-naphthalenecarboxamide (1.21 g) as a yellow powder.

^{1}H-NMR ($CDCl_3$) δ: 2.80-2.87 (4H, m), 3.07 (6H, m), 7.46-7.72 (7H, m), 7.91 (1H, d, J=8.4 Hz), 8.53 (1H, s).

4) Sodium triacetoxyhydroborate (398 mg, 1.87 mmol) was dissolved in a mixed solution of acetic acid (40 ml) and tetrahydrofuran (10 ml) under ice-cooling. N-(4-Bromophenyl)-6-[(dimethylamino)methylidene]-5-oxo-5,6,7,8-tetrahydro-2-naphthalenecarboxamide (500 mg,

1.25 mmol) obtained in 3) was added to the solution, which was stirred for 1 hour. The reaction mixture was concentrated under reduced pressure at room temperature. 2-Propanol (50 ml) was added to the residue, and sodium borohydride (142 mg, 3.75 mmol) was further added under ice-cooling. After stirring for 2 hours, the reaction mixture was concentrated. Sodium hydrogencarbonate solution and ethyl acetate was added to the residue for liquid separation. The organic layer was concentrated. The residue was dissolved in a mixed solution of acetic acid (20 ml) and concentrated hydrochloric acid (20 ml), which was stirred at 70℃ for 5 hours. The reaction mixture was concentrated. 4N aqueous sodium hydroxide solution and ethyl acetate were added to the residue, and extraction was conducted. The organic layer was washed with water, and concentrated. The residue was purified by alumina column chromatography (development solvent : ethyl acetate), and the eluent was washed with diisopropyl ether, to give the titled compound (234 mg) as a white powder.

^{1}H-NMR ($CDCl_3$) δ : 2.26 (6H, s), 2.38 (2H, t, J=8.1 Hz), 2.89 (2H, t, J=8.1 Hz), 3.02 (2H, s), 6.42 (1H, s), 7.10 (1H, d, J=8.6 Hz), 7.47 (2H, d, J=8.9 Hz), 7.55 (2H, d J=8.9 Hz), 7.61 (1H, s), 7.62 (1H, d, J=6.7 Hz), 7.76 (1H, s).

Elemental analysis for $C_{20}H_{21}BrN_2O$

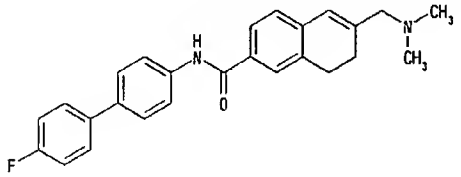
Calcd. : C, 62.35; H, 5.49; N, 7.27.

Found : C, 61.98; H, 5.43; N, 7.07.

Melting point: 175 - 179°C (crystallization solvent : diisopropyl ether)

Example 102

6-[(Dimethylamino)methyl]-N-(4'-fluoro[1,1'-biphenyl]-4-yl)-7,8-dihydro-2-naphthalenecarboxamide



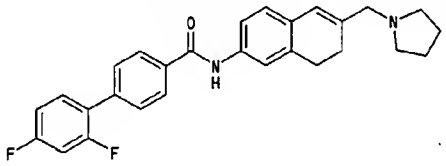
The titled compound was obtained as a white powder, by the same method as in Example 16, using N-(4-bromophenyl)-6-[(dimethylamino)methyl]-7,8-dihydro-2-naphthalenecarboxamide (170 mg, 0.44 mmol) obtained in Example 101 and 4-fluorophenylboric acid (74 mg, 0.53 mmol).

^{1}H-NMR ($CDCl_3$) δ: 2.27 (6H, s), 2.39 (2H, t, J=8.4 Hz), 2.91(2H, t, J=8.4 Hz), 3.02 (2H, s), 6.43 (1H, s), 7.09-7.16 (3H, m), 7.52-7.73 (8H, m), 7.81 (1H, s).

Melting point: 200 - 204°C (crystallization solvent : diisopropyl ether)

Example 103

2',4'-Difluoro-N-[6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained as a white powder by the same method as in Example 1, using 6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 54.

^{1}H-NMR ($CDCl_3$) δ: 1.75-1.90 (4H, m), 2.36 (2H, t, J=8.1 Hz), 2.45-2.60 (4H, m), 2.85 (2H, t, J=8.1 Hz), 3.18 (2H, s), 6.36 (1H, s), 6.92-7.03 (3H, m), 7.36-7.45 (2H, m), 7.48 (1H, s), 7.62 (2H, d, J=8.4 Hz), 7.78 (1H, s), 7.94 (2H, d, J=8.4 Hz).

Elemental analysis for $C_{28}H_{26}F_2N_2O$

Calcd.: C, 75.66; H, 5.90; N, 6.30.

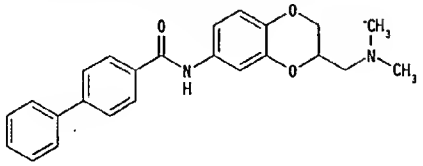
Found: C, 75.36; H, 5.92; N, 6.10.

Melting point: 165 - 167°C (crystallization solvent : diisopropyl ether)

Example 104

N-[3-[(Dimethylamino)methyl]-2,3-dihydro-1,4-

benzodioxin-6-yl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained as a white powder by the same method as in Example 1, using N,N-dimethyl-N-[(7-amino-2,3-dihydro-1,4-benzodioxin-2-yl)methyl]amine obtained in Reference Example 62.

^{1}H-NMR ($CDCl_3$) δ : 2.33 (6H, s), 2.48-2.66 (2H, m), 3.93-3.99 (1H, m), 4.27-4.31 (2H, m), 6.86(1H, d, J=8.6 Hz), 7.03-7.07 (1H, m), 7.31-7.32 (1H, m), 7.37-7.49 (3H, m), 7.62 (2H, d, J=7.0 Hz), 7.68 (2H, d, J=8.4Hz), 7.76 (1H, s), 7.91 (2H, d, J=8.4 Hz).

Elemental analysis for $C_{24}H_{24}N_2O_3$

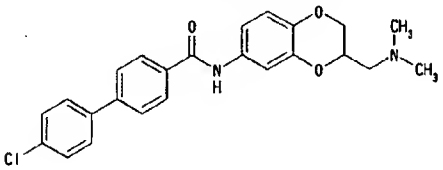
Calcd. : C, 74.21; H, 6.23; N, 7.21.

Found : C, 74.17; H, 6.23; N, 7.01.

Melting point: 124 - 126°C (crystallization solvent : diisopropyl ether)

Example 105

4'-Chloro-N-[3-[(dimethylamino)methyl]-2,3-dihydro-1,4-benzodioxin-6-yl][1,1'-biphenyl]-4-carboxamide



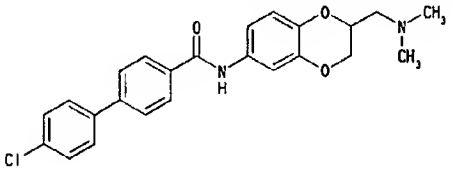
The titled compound was obtained as a white powder by the same method as in Example 1, using N,N-dimethyl-N-[(7-amino-2,3-dihydro-1,4-benzodioxin-2-yl)methyl]amine obtained in Reference Example 62.

^{1}H-NMR ($CDCl_3$) δ : 2.33 (6H, s), 2.50-2.67 (2H, m), 3.94-4.01 (1H, m), 4.28-4.31 (2H, m), 6.86 (1H, d, J=8.7 Hz), 7.03-7.06 (1H, m), 7.31 (1H, m), 7.44 (2H, d, J=8.4 Hz), 7.55 (2H, d, J=8.4 Hz), 7.65 (2H, d, J=8.1 Hz), 7.67 (1H, s), 7.91 (2H, d, J=8.1 Hz).

Melting point: 158 - 159°C (crystallization solvent : diisopropyl ether)

Example 106

4'-Chloro-N-[2-[(dimethylamino)methyl]-2,3-dihydro-1,4-benzodioxin-6-yl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained as a white powder by the same method as in Example 1, using N,N-dimethyl-N-[(6-amino-2,3-dihydro-1,4-benzodioxin-2-yl)methyl]amine obtained in Reference Example 63.

^{1}H-NMR ($CDCl_3$) δ : 2.34 (6H, s), 2.46-2.67 (2H, m), 3.94-4.01 (1H, m), 4.28-4.34 (2H, m), 6.91 (1H, d, J=8.6 Hz), 7.02-7.05 (1H, m), 7.30 (1H, m), 7.44 (2H, d, J=8.4 Hz), 7.55 (2H, d, J=8.4 Hz), 7.66 (2H, d, J=8.1 Hz), 7.70 (1H, s), 7.92 (2H, d, J=8.1 Hz).

Elemental analysis for $C_{24}H_{23}ClN_2O_3$

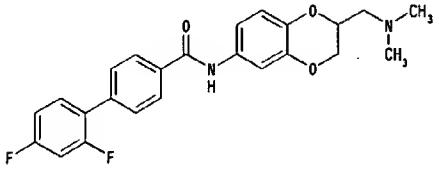
Calcd. : C, 68.16; H, 5.48; N, 6.62.

Found : C, 68.09; H, 5.29; N, 6.57.

Melting point: 215 - 217°C (crystallization solvent : diisopropyl ether)

Example 107

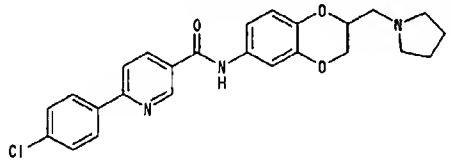
2',4'-Difluoro-N-[2-[(dimethylamino)methyl]-2,3-dihydro-1,4-benzodioxin-6-yl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained as a white powder by the same method as in Example 1, using N,N-dimethyl-N-[(6-amino-2,3-dihydro-1,4-benzodioxin-2-yl)methyl]amine

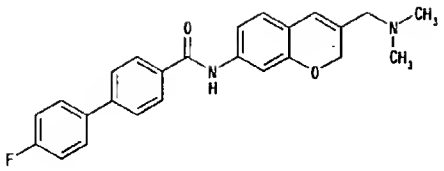
obtained in Reference Example 63.
^{1}H-NMR ($CDCl_3$) δ : 2.34 (6H, s), 2.50-2.63 (2H, m), 3.94-4.01 (1H, m), 4.28-4.34 (2H, m), 6.91 (1H, d, J=8.6 Hz), 6.91-7.03 (3H, m), 7.30 (1H, m), 7.40-7.50 (1H, m), 7.61 (2H, d, J=8.1 Hz), 7.69 (1H, s), 7.92 (2H, d, J=8.1 Hz).
Elemental analysis for $C_{24}H_{22}F_2N_2O_3$
Calcd. : C, 67.91; H, 5.22; N, 6.60.
Found : C, 67.75; H, 5.09; N, 6.48.
Melting point: 209 - 210°C (crystallization solvent : diisopropyl ether)

Example 108
6-(4-Chlorophenyl)-N-[2-(1-pyrrolidinylmethyl)-2,3-dihydro-1,4-benzodioxin-6-yl]nicotinamide



The titled compound was obtained as a white powder by the same method as in Example 1, using 1-[(6-amino-2,3-dihydro-1,4-benzodioxin-2-yl)methyl]pyrrolidine obtained in Reference Example 64.
^{1}H-NMR ($CDCl_3$) δ : 1.81 (4H, m), 2.50-2.63 (4H, m), 2.75-2.77 (2H, m), 3.90-4.10 (1H, m), 4.30-4.36 (2H, m), 6.91 (1H, d, J=8.6 Hz), 7.00-7.10 (1H, m), 7.26 (1H, m), 7.48 (2H, d, J=8.6 Hz), 7.72 (1H, s), 7.81 (1H, d, J=7.8 Hz), 8.01 (2H, d, J=8.6 Hz), 8.20-8.25 (1H, m), 9.10 (1H, s).
Elemental analysis for $C_{25}H_{24}ClN_3O_3$
Calcd. : C, 66.74; H, 5.38; N, 9.34.
Found : C, 66.66; H, 5.46; N, 9.11.
Melting point: 218 - 220°C (crystallization solvent : diisopropyl ether)

Example 109
N-[3-[(Dimethylamino)methyl]-2H-chromen-7-yl]-4'-fluoro[1,1'-biphenyl]-4-carboxamide



The titled compound was obtained by carrying out the same operation as in Example 1, using 3-[(N,N-dimethylamino)methyl]-2H-chromen-7-amine obtained in Reference Example 59.

^{1}H-NMR ($CDCl_3$) δ : 2.23 (6H, s), 2.97 (2H, s), 4.79 (2H, s), 6.30 (1H, s), 6.96 (1H, d, J=8.1 Hz), 7.13-7.22 (4H, m), 7.56-7.61(2H, m), 7.65 (2H, d, J=8.4 Hz), 7.78 (1H, s), 7.92 (2H, d, J=8.4 Hz).

Elemental analysis for $C_{25}H_{23}FN_2O_2$

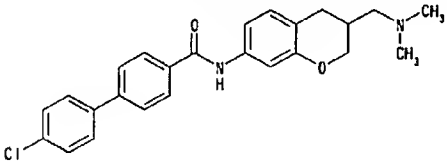
Calcd. : C, 74.61; H, 5.76; N, 6.96.

Found : C, 74.35; H, 5.68; N, 6.74.

Melting point: 192 - 195°C (crystallization solvent : diisopropyl ether)

Example 110

4'-Chloro-N-[3-[(dimethylamino)methyl]-3,4-dihydro-2H-chromen-7-yl][1,1'-biphenyl]-4-carboxamide

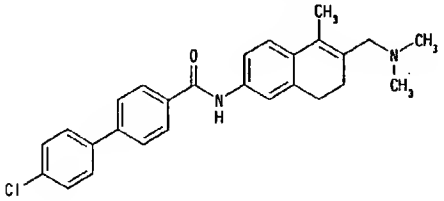


The titled compound was obtained by carrying out the same operation as in Example 1, using N-[(7-amino-3,4-dihydro-2H-chromen-3-yl)methyl]-N,N-dimethylamine obtained in Reference Example 65.

^{1}H-NMR ($CDCl_3$) δ : 2.26 (6H, s), 2.27 (3H, m), 2.47-2.51 (1H, m), 2.83-2.89 (1H, m), 3.82-3.86 (1H, m), 4.28-4.32 (1H, m), 7.04 (1H, d, J=8.1 Hz), 7.12-7.18 (2H, m), 7.44 (2H, d, J=8.4 Hz), 7.56 (2H, d, J=8.4 Hz), 7.67 (2H, d, J=8.4 Hz), 7.71 (1H, s), 7.93 (2H, d, J=8.4 Hz).

Example 111

4'-Chloro-N-[6-[(dimethylamino)methyl]-5-methyl-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained by carrying out the same operation as in Example 1, using 6-[(dimethylamino)methyl]-5-methyl-7,8-dihydro-2-naphthalenamine obtained in Reference Example 66.

^{1}H-NMR ($CDCl_3$) δ : 2.09 (3H, s), 2.27 (6H, s), 2.31-2.37 (2H, m), 2.74-2.79 (2H, m), 3.08 (2H, s), 7.27-7.30 (1H, m), 7.44-7.48 (4H, m), 7.56 (2H, d, J=8.6 Hz), 7.67 (2H, d, J=8.4 Hz), 7.79 (1H, s), 7.95 (2H, d, J=8.4 Hz).

Elemental analysis for $C_{27}H_{27}ClN_2O$

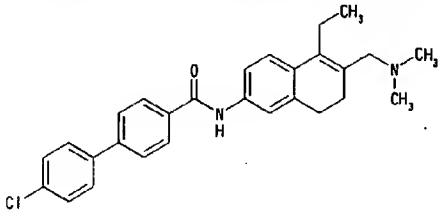
Calcd. : C, 75.25; H, 6.31; N, 6.50.

Found : C, 74.86; H, 6.20; N, 6.42.

Melting point: 199 - 204°C (crystallization solvent : diisopropyl ether)

Example 112

4'-Chloro-N-[6-[(dimethylamino)methyl]-5-ethyl-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained by carrying out the same operation as in Example 1, using 6-[(dimethylamino)methyl]-5-ethyl-7,8-dihydro-2-naphthalenamine obtained in Reference Example 67.

^{1}H-NMR ($CDCl_3$) δ : 1.09 (3H, t, J=7.5 Hz), 2.27 (6H, s), 2.31-2.37 (2H, m), 2.60-2.63 (2H, m), 2.71-2.76 (2H, m), 3.08 (2H, s), 7.31 (1H, d, J=9.2 Hz), 7.43-7.49 (4H, m),

7.56 (2H, d, J=8.7 Hz), 7.67 (2H, d, J=8.6 Hz), 7.80 (1H, s), 7.94 (2H, d, J=8.6 Hz).

Elemental analysis for $C_{28}H_{29}ClN_2O$

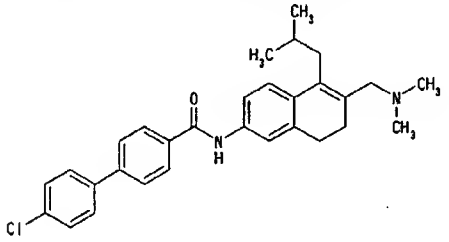
Calcd.: C, 75.57; H, 6.57; N, 6.30.

Found: C, 75.41; H, 6.34; N, 6.23.

Melting point: 201 - 204°C (crystallization solvent : diisopropyl ether)

Example 113

4'-Chloro-N-[6-[(dimethylamino)methyl]-5-isobutyl-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained by carrying out the same operation as in Example 1, using 6-[(dimethylamino)methyl]-5-isobutyl-7,8-dihydro-2-naphthalenamine obtained in Reference Example 68.

^{1}H-NMR ($CDCl_3$) δ: 0.90 (6H, d, J=6.4 Hz), 1.73-1.78 (1H, m), 2.23 (6H, s), 2.34 (2H, m), 2.50 (2H, d, J=7.3 Hz), 2.74 (2H, m), 3.13 (2H, s), 7.26-7.30 (1H, m), 7.45-7.48 (4H, m), 7.56 (2H, d, J=8.7 Hz), 7.67 (2H, d, J=8.4 Hz), 7.79 (1H, s), 7.94 (2H, d, J=8.4 Hz).

Elemental analysis for $C_{30}H_{33}ClN_2O$

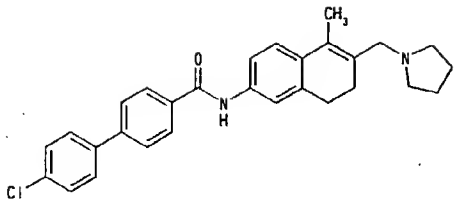
Calcd.: C, 76.17; H, 7.03; N, 5.92.

Found: C, 75.91; H, 7.19; N, 5.72.

Melting point: 159 - 162°C (crystallization solvent : diisopropyl ether)

Example 114

4'-Chloro-N-[5-methyl-6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



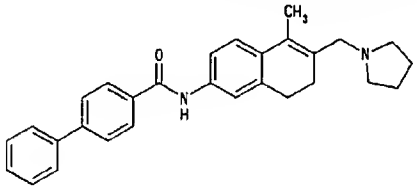
The titled compound was obtained by carrying out the same operation as in Example 1, using 5-methyl-6- (1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 69.

^{1}H-NMR ($CDCl_3$) δ: 1.79 (4H, m), 2.11 (3H, s), 2.30-2.40 (2H, m), 2.54 (4H, m), 2.74-2.79 (2H, m), 3.28 (2H, s), 7.26-7.30 (1H, m), 7.45-7.48 (4H, m), 7.56 (2H, d, J=8.6 Hz), 7.67 (2H, d, J=8.4 Hz), 7.81 (1H, s), 7.95 (2H, d, J=8.4 Hz).

Melting point: 190 - 192°C (crystallization solvent : diisopropyl ether)

Example 115

N-[5-Methyl-6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



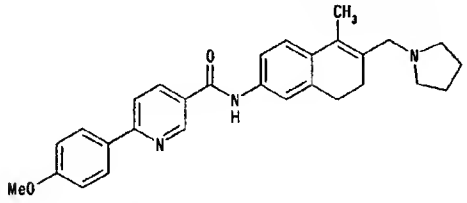
The titled compound was obtained by carrying out the same operation as in Example 1, using 5-methyl-6- (1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 69.

^{1}H-NMR ($CDCl_3$) δ: 1.78 (4H, m), 2.10 (3H, s), 2.35-2.40 (2H, m), 2.53 (4H, m), 2.70-2.78 (2H, m), 3.28 (2H, s), 7.26-7.28 (1H, m), 7.40-7.50 (5H, m), 7.62 (2H, d, J=7.0 Hz), 7.70 (2H, d, J=8.4 Hz), 7.87 (1H, s), 7.94 (2H, d, J=8.4 Hz).

Melting point: 169 - 170°C (crystallization solvent : diisopropyl ether)

Example 116

6-(4-Methoxyphenyl)-N-[5-methyl-6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl]nicotinamide



The titled compound was obtained by carrying out the same operation as in Example 1, using 5-methyl-6- (1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 69.

^{1}H-NMR ($CDCl_3$) δ : 1.78 (4H, m), 2.09 (3H, s), 2.35-2.40 (2H, m), 2.53 (4H, m), 2.70-2.77 (2H, m), 3.27 (2H, s), 3.88 (3H, s), 7.01 (2H, d, J=8.9 Hz), 7.26 (1H, d, J=8.9 Hz), 7.45-7.47 (2H, m), 7.75 (1H, d, J=8.4 Hz), 7.95 (1H, s), 8.01 (2H, d, J=8.9 Hz), 8.18-8.21 (1H, m), 9.09 (1H, m).

Elemental analysis for $C_{29}H_{31}N_3O_2$

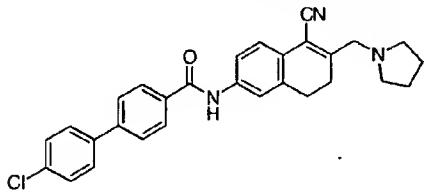
Calcd. : C, 76.79; H, 6.89; N, 9.26.

Found : C, 76.46; H, 6.64; N, 9.09.

Melting point: 165 - 167°C (crystallization solvent : diisopropyl ether)

Example 117

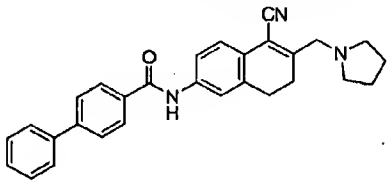
4'-Chloro-N-[5-cyano-6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained as a colorless powder by carrying out the same operation as in Example 1, using 6-amino-2-(1-pyrrolidinylmethyl)-3,4-dihydro-1-naphthalenecarbonitrile obtained in Reference Example 70 and 4'-chloro[1,1'-biphenyl]-4-carboxylic acid.

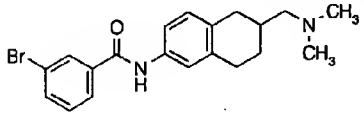
^{1}H NMR (DMSO-d_6) δ:1.73 (4H, m), 2.50 (4H, m), 2.56 (2H, m), 2.82 (2H, m), 3.49 (2H, s), 7.32 (1H, d, J = 9.0 Hz), 7.57 (2H, d, J = 8.4 Hz), 7.56-7.87 (6H, m), 8.07 (2H, d, J = 8.4 Hz), 10.40 (1H, s).
FABMS(pos) 468.2 $[M+H]^+$
Melting point: 191 - 192°C (crystallization solvent : diisopropyl ether)

Example 118
N-[5-Cyano-6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained by as a colorless powder carrying out the same operation as in Example 1, using 6-amino-2-(1-pyrrolidinylmethyl)-3,4-dihydro-1-naphthalenecarbonitrile obtained in Reference Example 70 and [1,1'-biphenyl]-4-carboxylic acid.
^{1}H NMR (DMSO-d_6) δ : 1.81 (4H, m), 2.62 (6H, m), 2.88 (2H, m), 3.56 (2H, s), 7.41 (2H, m), 7.46 (3H, m), 7.64 (2H, d, J = 6.9 Hz), 7.73 (3H, m), 7.88 (1H, s), 7.95 (2H, d, J = 8.1 Hz).
FABMS(pos) 434.2 $[M+H]^+$
Melting point: 168 - 170°C (crystallization solvent : diisopropyl ether)

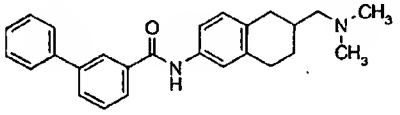
Example 119
3-Bromo-N-[6-[(dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]benzamide



The titled compound was obtained by carrying out the same operation as in Example 1, using 6-amino-2-[(N,N-

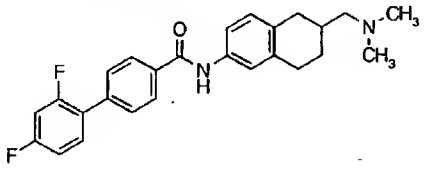
dimethylamino)methyl]tetralin and 3-bromobenzoic acid.
^{1}H NMR (DMSO-d_6) δ: 1.31 (1H, m), 1.89 (2H, m), 2.17 (6H, s), 2.17-2.35 (3H, m), 2.77 (3H, m), 7.04 (1H, d, J=8.4 Hz), 7.49 (3H, m), 7.79 (1H, d, J=8.1 Hz), 7.94 (1H, d, J=7.8 Hz), 8.13 (1H, s), 10.20 (1H, s).

Example 120
N-[6-[(Dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl][1,1'-biphenyl]-3-carboxamide



The titled compound was obtained by carrying out the same operation as in Example 16, using 3-bromo-N-[6-[(dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]benzamide obtained in Example 119 and phenylboronic acid.
^{1}H NMR (DMSO-d_6) δ: 1.43 (1H, m), 2.02 (1H, m), 2.21 (1H, m), 2.42 (1H, m), 2.81 (6H, s), 2.88 (3H, m), 3.09 (2H, m), 7.06 (1H, m), 7.42-7.65 (6H, m), 7.78-7.95 (4H, m), 8.22 (1H, s), 10.27 (1H, s).
FABMS(pos) 385.2 $[M+H]^+$
Melting point: 145 - 148°C (crystallization solvent : ethyl acetate-diisopropyl ether)

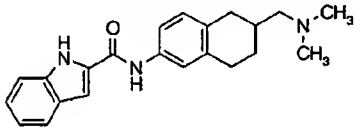
Example 121
N-[6-[(Dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]-2',4'-difluoro[1,1'-biphenyl]-4-carboxamide



The titled compound was obtained by carrying out the same operation as in Example 1, using 6-amino-2-[(N,N-dimethylamino)methyl]tetralin and 2', 4'-difluoro[1,1'-

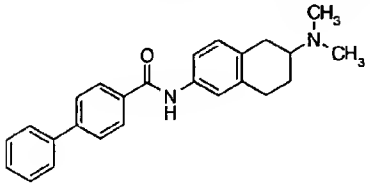
biphenyl]-4-carboxylic acid.
^{1}H NMR ($CDCl_3$) δ : 1.41 (1H, m), 1.94 (2H, m), 2.25 (6H, s), 2.23-2.30 (3H, m), 2.86 (3H, m), 6.96 (2H, m), 7.09 (1H, d, J=8.1 Hz), 7.30 (1H, m), 7.43 (2H, m), 7.61 (2H, m), 7.76 (1H, s), 7.93 (2H, m).
Melting point: 162 - 163°C (crystallization solvent : ethyl acetate-diisopropyl ether)

Example 122
N-[6-[(Dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl-1H-indole-2-carboxamide



The titled compound was obtained by carrying out the same operation as in Example 1, using 6-amino-2-[(N,N-dimethylamino)methyl]tetralin and 1H-indol-2-carboxylic acid.
^{1}H NMR (DMSO-d_6) δ : 1.32 (1H, m), 1.91 (2H, m), 2.16 (6H, s), 2.16-2.35 (3H, m), 2.78 (3H, m), 7.06 (2H, m), 7.21 (1H, m), 7.44 (4H, m), 7.66 (1H, d, J=8.1 Hz), 10.05 (1H, s), 11.68 (1H, s).
FABMS(pos) 348.2 $[M+H]^+$
Melting point: 190 - 192°C (crystallization solvent : ethyl acetate - diisopropyl ether)

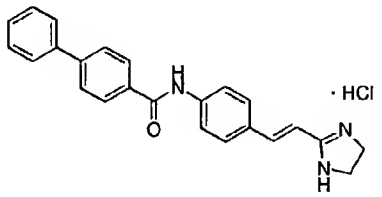
Example 123
N-[6-[(Dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl] [1,1'-biphenyl]-4-carboxamide



A tetrahydrofuran solution (0.146ml, 0.293mmol) of N-(6-oxo-5,6,7,8-tetrahydro-2-naphthalenyl)[1,1'-

biphenyl]-4-carboxamide (10 mg, 0.029 mmol) obtained in Reference Example 72 and 2N dimethylamine was added to acetic acid−tetrahydrofuran (1:1) solution (0.5ml), which was stirred at 50℃ for 15 minutes. After the reaction mixture was cooled at room temperature, sodium triacetoxyhydroborate (31 mg, 0.146 mmol) was added, which was stirred at 50℃ for 2 hours. 1N Hydrochloric acid was added to the reaction mixture, which was washed with ethyl acetate. Sodium carbonate was added to the water layer to make it alkaline, then extraction was conducted using ethyl acetate. The extract was washed with saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then the solvent was distilled out under reduced pressure. The resulting residue was purified by alumina B column chromatography (development solvent; ethyl acetate), to give the titled compound (1.6mg).
^{1}H NMR ($CDCl_3$) δ: 1.68 (1H, m), 2.27 (1H, m), 2.40 (6H, s), 2.78 (5H, m), 7.11 (1H, d, J=8.1 Hz), 7.32-7.50 (5H, m), 7.62 (2H, m), 7.72 (2H, d, J=8.4 Hz), 7.78 (1H, br), 7.94 (2H, d, J=8.4 Hz).
FABMS(pos) 371.2 [M+H]+

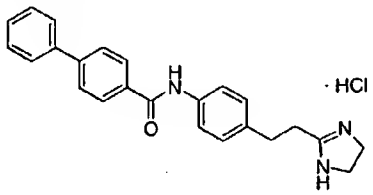
Example 124
N-[4-[(E)-2-(4,5-Dihydro-1H-imidazol-2-yl)ethenyl]phenyl][1,1'-biphenyl]-4-carboxamide hydrochloride



10.1 N Hydrogen chloride−ethanol solution (30 ml) was added to an ethanol suspension of N-[4-[(E)-2-cyanoethenyl]phenyl][1,1'-biphenyl]-4-carboxamide (250 mg, 0.771 mmol) obtained in Reference Example under room temperature, which was stirred for 16 hours. After the

solvent was distilled out under reduced pressure, ethanol was again added to the residue, and then ethylenediamine (0.155 ml, 2.31 mmol) was added at room temperature, which was stirred for 16 hours. Sodium hydrogencarbonate solution was added to the reaction mixture, and the precipitated crude product was washed with water and chloroform. This product was dissolved in methanol. 1 N Hydrochloric acid (4 ml) was added to the solution, and the solvent was distilled out under reduced pressure. Small amount of water was added to the resulting residue, to give the titled compound (124 mg) as a colorless powder.
^{1}H NMR (DMSO-d_6, free base) δ: 3.33 (4H, m), 6.61 (1H, d, J = 16.8 Hz), 7.15 (1H, d, J = 16.8 Hz), 7.52 (5H, m), 7.83 (6H, m), 8.07 (2H, d, J = 8.4 Hz).
Elemental analysis for $C_{24}H_{21}N_3O \cdot HCl \cdot 1.5H_2O$
Calcd.: C, 66.89; H, 5.85; N, 9.75.
Found: C, 67.16; H, 6.10; N, 10.03.

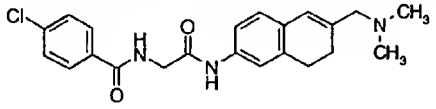
Example 125
N-[4-[2-(4,5-Dihydro-1H-imidazol-2-yl)ethenyl]phenyl][1,1'-biphenyl]-4-carboxamide hydrochloride



10% Palladium — carbon (200 mg) was added to a methanol suspension of N-[4-[(E)-2-(4,5-dihydro-1H-imidazol-2-yl)ethenyl]phenyl][1,1'-biphenyl]-4-carboxamide hydrochloride (80 mg, 0.198 mmol) obtained in Example 124, which was stirred under hydrogen atmosphere at 60℃ for 2 hours. After a catalyst was filtered off, the solvent was distilled out under reduced pressure. Diethyl ether was added to the resulting residue, to give the titled compound (52 mg) as a colorless powder.

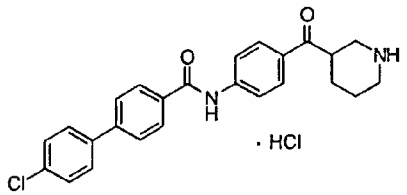
^{1}H NMR (DMSO-d_6) δ : 2.73-2.97 (4H, m), 3.37 (4H, s), 7.24 (2H, d, J = 8.4 Hz), 7.46 (3H, m), 7.76 (6H, m), 8.08 (2H, d, J = 8.4 Hz).
FABMS(pos) 370[M+H]$^+$

Example 126
4-Chloro-N-[2-[[6-[(dimethylamino)methyl]-7,8-dihydro-2-naphthalenyl]amino]-2-oxoethyl]benzamide



The titled compound was obtained by carrying out the same operation as in Example 1, using 6- [(N,N-dimethylamino)methyl]-7,8-dihydro-2-naphthalenamine obtained in Example 41-2) and 4-chlorobenzoyl glycine.
^{1}H NMR (DMSO-d_6) δ : 2.18 (6H, s), 2.21 (2H, m), 2.71 (2H, m), 2.91 (2H, s), 4.05 (2H, d, J=5.6 Hz), 6.30 (1H, s), 6.98 (1H, d, J=8.1 Hz), 7.36 (2H, m), 7.58 (2H, d, J=8.4 Hz), 7.92 (2H, d, J=8.4 Hz), 8.94 (1H, t, J=5.6 Hz), 10.00 (1H, s).
FABMS(pos) 398 [M+H]$^+$
Melting point: 168 - 171°C (crystallization solvent : diisopropyl ether)

Example 127
4'-Chloro-N-[4-(3-piperidinylcarbonyl)phenyl][1,1'-biphenyl]-4-carboxamide hydrochloride

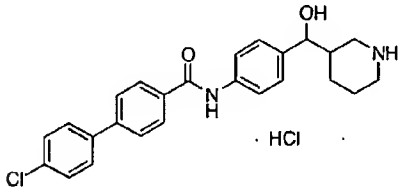


1) tert-Butyl 3-[4-[[(4'-chloro[1,1'-biphenyl]-4-yl)carbonyl]amino]benzoyl]-1-piperidinecarboxylate was obtained by carrying out the same operation as in Example 1, using tert-butyl 3-(4-aminobenzoyl)-1-piperidinecarboxylate obtained in Reference Example 77 and

4'-chloro[1,1'-biphenyl]-4-carboxylic acid.
FABMS(pos) 519.2 [M+H]+

2) 4N Hydrogen chloride−ethyl acetate (1 ml) was added to tert-butyl 3-[4-[[(4'-chloro[1,1'-biphenyl]-4-yl)carbonyl]amino]benzoyl]-1-piperidinecarboxylate (100 mg, 0.193 mmol) obtained in 1). One hour later, the solvent was distilled out under reduced pressure. Diisopropyl ether was added to the residue, to give the titled compound (73.3 mg) as a colorless powder.
^{1}H NMR (DMSO-d_6) δ : 1.56 (1H, m), 1.82 (2H, m), 2.02 (1H, m), 2.89 (1H, m), 3.05 (1H, m), 3.33 (2H, m), 3.90 (1H, m), 7.58 (2H, d, J=8.1Hz), 7.81 (2H, d, J=8.1Hz), 7.88 (2H, d, J=8.1Hz), 8.03 (4H, m), 8.11 (2H, d, J=8.1Hz), 9.04 (2H, br), 10.73 (1H, s).
FABMS(pos) 419.2 $[M+H]^+$
Melting point: 222 - 225°C (decomposition)

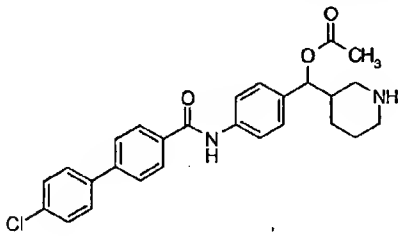
Example 128
4'-Chloro-N-[4-[hydroxy(3-piperidinyl)methyl]phenyl][1,1'-biphenyl]-4-carboxamide hydrochloride



4N Hydrogen chloride−ethyl acetate (1 ml) was added to tert-butyl 3-[[4-[[(4'-chloro[1,1'-biphenyl]-4-yl)carbonyl]amino]phenyl](hydroxy)methyl]-1-piperidinecarboxylate (100 mg, 0.192 mmol) obtained in Reference Example 78. One hour later, the solvent was distilled out under reduced pressure. Diisopropyl ether was added to the residue, to give the titled compound (79.8 mg) as a colorless powder.
FABMSMS(pos) 421.2 $[M+H]^+$
Melting point: 195°C (decomposition)

Example 129

[4-[[(4'-Chloro[1,1'-biphenyl]-4-yl)carbonyl]amino]phenyl](3-piperidinyl)methyl acetate



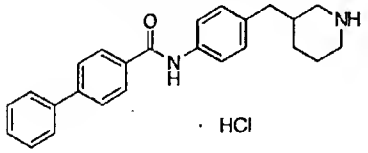
Concentrated sulfuric acid (0.0562 ml) was added to an acetic acid solution (3.5 ml) of tert-butyl 3-[[4-[[(4'-chloro[1,1'-biphenyl]-4-yl)carbonyl]amino]phenyl](hydroxy)methyl]-1-piperidinecarboxylate (366 mg, 0.702 mmol) obtained in Example 128, which was stirred under room temperature for 16 hours. Ethyl acetate was added to the reaction mixture, which was washed with potassium hydrogencarbonate solution and saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then the solvent was distilled out under reduced pressure. The resulting oily substance was purified by alumina B column chromatography (development solvent ; ethyl acetate : methanol = 3:1), and powdered with diisopropyl ether, to give the titled compound (210 mg).

FABMS(pos) 403.2 $[M+H]^+$

Melting point: 200 - 203°C.

Example 130

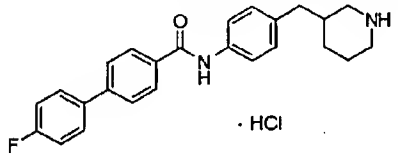
N-[4-(3-Piperidinylmethyl)phenyl][1,1'-biphenyl]-4-carboxamide hydrochloride



4N Hydrogen chloride−ethyl acetate (2 ml) was added to tert-butyl 3-[4-[([1,1'-biiphenyl]-4-

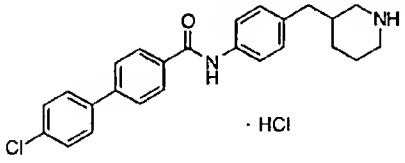
ylcarbonyl)amino]benzyl]-1-piperidinecarboxylate (100 mg, 0.212 mmol) obtained in Reference Example 80. Two hours later, the solvent was distilled out under reduced pressure. Diisopropyl ether was added to the residue for powdering, to give the titled compound (79 mg).
FABMS(pos) 371.3 $[M+H]^+$
Melting point: 218 - 220°C (decomposition)

Example 131
4'-Fluoro-N-[4-(3-piperidinylmethyl)phenyl][1,1'-biphenyl]-4-carboxamide hydrochloride



4N Hydrogen chloride−ethyl acetate (3 ml) was added to tert-butyl 3-[4-[[(4'-fluoro[1,1'-biphenyl]-4-yl)carbonyl]amino]benzyl]-1-piperidinecarboxylate (150 mg, 0.307 mmol) obtained in Reference Example 81. Two hours later, the solvent was distilled out under reduced pressure. Diisopropyl ether was added to the residue, to give the titled compound (115 mg) as a colorless powder.
FABMS(pos) 389.3 $[M+H]^+$
Melting point: 205°C (decomposition)

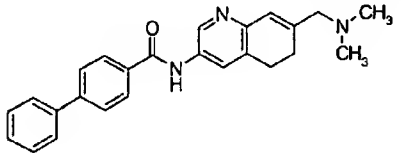
Example 132
4'-Chloro-N-[4-(3-piperidinylmethyl)phenyl][1,1'-biphenyl]-4-carboxamide hydrochloride



4N Hydrogen chloride−ethyl acetate (3 ml) was added to tert-butyl 3-[4-[[(4'-chloro[1,1'-biphenyl]-4-yl)carbonyl]amino]benzyl]-1-piperidinecarboxylate (150 mg, 0.297 mmol)obtained in Reference Example 82. Two hours

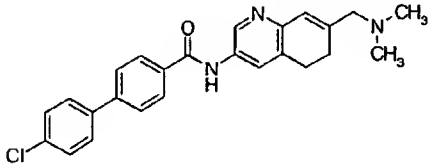
later, the solvent was distilled out under reduced pressure. Diisopropyl ether was added to the residue, to give the titled compound (73.3 mg) as a colorless powder.
FABMS(pos) 405.2 [M+H]+
Melting point: 200°C (decomposition)

Example 133
N-[7-[(Dimethylamino)methyl]-5,6-dihydro-3-quinolinyl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained by carrying out the same operation as in Example 1, using N-[(3-amino-5,6-dihydro-7-quinolinyl)methyl]-N,N-dimethylamine obtained in Reference Example 86 and [1,1'-biphenyl]-4-carboxylic acid.
^{1}H NMR (DMSO-d_6) δ : 2.16 (6H, s), 2.29 (2H, t, J=8.1 Hz), 2.84 (2H, t, J=8.1 Hz), 2.98 (2H, s), 6.40 (1H, s), 7.42 (1H, m), 7.51 (2H, m), 7.76 (2H, d, J=7.2 Hz), 7.84 (2H, d, J=8.1 Hz), 7.97 (1H, s), 8.06 (2H, d, J=8.4 Hz), 8.65 (1H, s), 10.39 (1H, s).
FABMS(pos) 384.2 [M+H]+
Melting point: 202 - 203°C.

Example 134
4'-Chloro-N-[7-[(dimethylamino)methyl]-5,6-dihydro-3-quinolinyl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained by carrying out the same operation as in Example 1, using N-[(3-amino-5,6-dihydro-7-quinolinyl)methyl]-N,N-dimethylamine obtained

in Reference Example 86 and 4'-chloro[1,1'-biphenyl]-4-carboxylic acid.

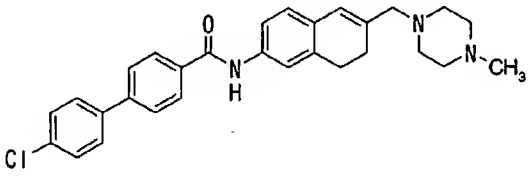
^{1}H NMR (DMSO-d_6) δ : 2.17 (6H, s), 2.31 (2H, t, J=8.1 Hz), 2.85 (2H, t, J=8.1 Hz), 2.99 (2H, s), 6.41 (1H, s), 7.57 (2H, d, J=8.4 Hz), 7.81 (2H, d, J=8.4 Hz), 7.86 (2H, d, J=8.4 Hz), 7.98 (1H, s), 8.08 (2H, d, J=8.4 Hz), 8.66 (1H, s), 10.41 (1H, s).

FABMS(pos) 418.2 $[M+H]^+$

Melting point: 220 - 222°C.

Example 135

4'-Chloro-N-[6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



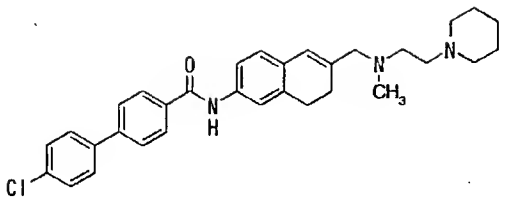
The titled compound was obtained by carrying out the same operation as in Example 51, using 4'-chloro-N-[6-(chloromethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide obtained in Reference Example 56.

1H-NMR (CDCl3) δ : 2.30 (3H, s), 2.25-2.50 (10H, m), 2.83 (2H, t, J = 8.1 Hz), 3.07 (2H, s), 6.35 (1H, s), 7.01 (1H, d, J = 8.1 Hz), 7.36 (1H, d, J = 7.8 Hz), 7.44 (2H, d, J = 8.4 Hz), 7.51 (1H, s), 7.55 (2H, d, J = 8.4 Hz), 7.66 (2H, d, J = 8.4 Hz), 7.84 (1H, s), 7.93 (2H, d, J = 8.4 Hz).

Melting point: 220 - 222°C (crystallization solvent : tetrahydrofuran - n-hexane)

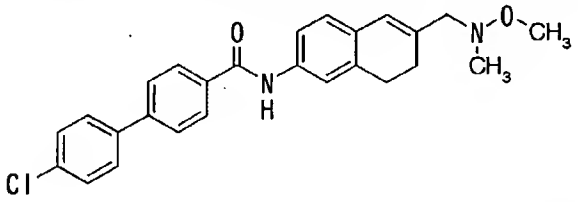
Example 136

4'-Chloro-N-[6-[[methyl[2-(1-piperidinyl)ethyl]amino]methyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained by carrying out the same operation as in Example 51, using 4'-chloro-N-[6-(chloromethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide obtained in Reference Example 56.
^{1}H-NMR ($CDCl_3$) δ : 1.72-1.77 (6H, m), 2.25-2.36 (2H, m), 2.27 (3H, s), 2.52-2.63 (8H, m), 2.84 (2H, t, J = 8.0 Hz), 3.08 (2H, s), 6.35 (1H, s), 7.01 (1H, d, J = 8.1 Hz), 7.38 (1H, d, J = 8.1 Hz), 7.44 (2H, d, J = 8.4 Hz), 7.49 (1H, s), 7.55 (2H, d, J = 8.4 Hz), 7.66 (2H, d, J = 8.4 Hz), 7.83 (1H, s), 7.93 (2H, d, J = 8.4 Hz).
Melting point: 165 - 167°C (crystallization solvent : tetrahydrofuran - n-hexane)

Example 137
4'-Chloro-N-[6-[[methoxy(methyl)amino]methyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide

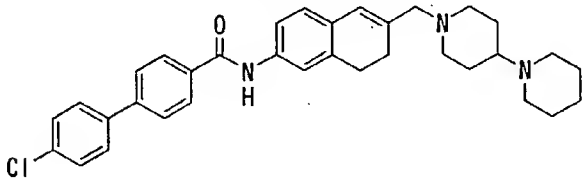


The titled compound was obtained by carrying out the same operation as in Example 51, using 4'-chloro-N-[6-(chloromethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide obtained in Reference Example 56.
^{1}H-NMR ($CDCl_3$) δ : 2.41 (2H, t, J = 8.1 Hz), 2.61 (3H, s), 2.86 (2H, t, J = 8.1 Hz), 3.37 (2H, s), 3.52 (3H, s), 6.39 (1H, s), 7.03 (1H, d J = 8.1 Hz), 7.36 (1H, d, J = 8.1 Hz), 7.44 (2H, d, J = 8.4 Hz), 7.53 (1H, s), 7.55 (2H, d, J = 8.4 Hz), 7.66 (2H, d, J = 8.4 Hz), 7.83 (1H, s), 7.93 (2H, d, J = 8.4 Hz).

Melting point: 190 - 192°C (crystallization solvent : ethyl acetate - n-hexane)

Example 138

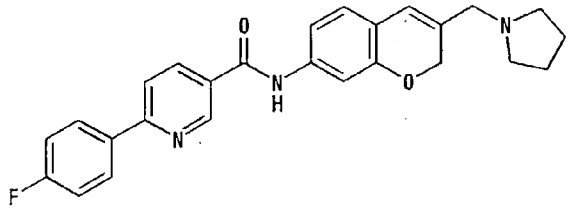
4'-Chloro-N-[6-[[4-(1-piperidinyl)-1-piperidinyl]methyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained by carrying out the same operation as in Example 51, using 4'-chloro-N-[6-(chloromethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide obtained in Reference Example 56.
^{1}H-NMR ($CDCl_3$) δ : 1.45-1.96 (12H, m), 2.29-2.34 (3H, m), 2.57 (4H, s), 2.83 (2H, t, J = 8.1 Hz), 2.96-3.03 (4H, m), 6.32 (1H, s), 7.00 (1H, d, J = 8.1 Hz), 7.38 (1H, d, J = 8.1 Hz), 7.44 (2H, d, J = 8.4 Hz), 7.50 (1H, s), 7.55 (2H, d, J = 8.4 Hz), 7.66 (2H, d, J = 8.4 Hz), 7.86 (1H, s), 7.93 (2H, d, J = 8.4 Hz).
Melting point: 232 - 234°C (crystallization solvent : ethyl acetate - n-hexane)

Example 139

6-(4-Fluorophenyl)-N-[3-(1-pyrrolidinylmethyl)-2H-chromen-7-yl]nicotineamide



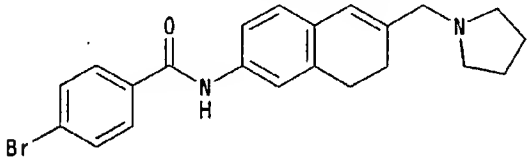
The titled compound was obtained by carrying out the same operation as in Example 1, using 3-(1-pyrroidinylmethyl)-2H-chromen-7-amine obtained in Reference Example 87.

^{1}H-NMR ($CDCl_3$) δ : 1.70(4H,s), 2.43 (4H, s), 3.12 (2H, s), 4.73 (2H, s), 6.37 (1H, s), 7.03 (1H, d, J = 7.8 Hz), 7.29-7.40 (4H, m), 8.15 (1H, d, J = 8.4 Hz), 8.22-8.39 (3H, m), 9.15 (1H, s), 10.40 (1H, s).

Melting point: 233 - 235°C (crystallization solvent : tetrahydrofuran - n-hexane)

Example 140

4-Bromo-N-[6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl]benzamide



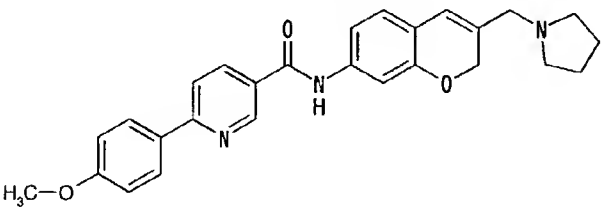
The titled compound was obtained by carrying out the same operation as in Example 1, using 6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 54.

^{1}H-NMR ($CDCl_3$) δ : 1.79 (4H, s), 2.35 (2H, t, J = 8.1 Hz), 2.52 (4H, s), 2.83 (2H, t, J = 8.1 Hz), 3.17 (2H, s), 6.35 (1H, s), 6.99 (1H, d, J = 8.1 Hz), 7.34 (1H, d, J = 8.1 Hz), 7.43 (1H, s), 7.60 (2H, d, J = 8.4 Hz), 7.72 (2H, d, J = 8.4 Hz), 7.76 (1H, s).

Melting point: 135 - 137°C (crystallization solvent : ethyl acetate - n-hexane)

Example 141

6-(4-Methoxyphenyl)-N-[3-(1-pyrrolidinylmethyl)-2H-chromen-7-yl]nicotinamide



The titled compound was obtained by carrying out the same operation as in Example 1, using 3-(1-

pyrrolidinylmethyl)-2H-chromen-7-amine obtained in Reference Example 87.

^{1}H-NMR ($CDCl_3$) δ : 1.70 (4H, s), 2.44 (4H, s), 3.12 (2H, s), 3.84 (3H, s), 4.73 (2H, s), 6.37 (1H, s), 7.03 (1H, d, J = 8.1 Hz), 7.09 (2H, t, J = 8.7 Hz), 7.29 (1H, d, J = 8.4 Hz), 7.31 (1H, s), 8.07 (1H, d, J = 8.7 Hz), 8.16 (2H, d, J = 8.7 Hz), 8.32 (1H, d, J = 8.4 Hz), 9.12 (1H, s), 10.34 (1H, s).

Elemental analysis for $C_{27}H_{27}N_3O_3$

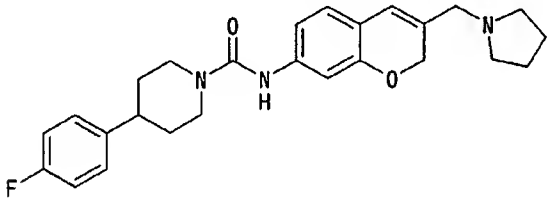
Calcd. : C, 73.45; H, 6.16; N, 9.52.

Found : C, 73.02; H, 6.27; N, 9.33.

Melting point: 243 - 245°C (crystallization solvent : tetrahydrofuran - n-hexane)

Example 142

4-(4-Fluorophenyl)-N-[3-(1-pyrrolidinylmethyl)-2H-chromen-7-yl]-1-piperidinecarboxamide



The titled compound was obtained by carrying out the same operation as in Example 99, using 3-(1-pyrrolidinylmethyl)-2H-chromen-7-amine obtained in Reference Example 87.

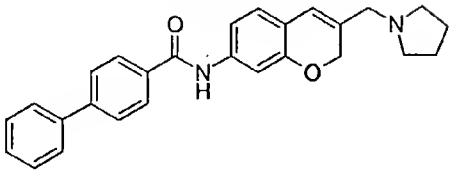
^{1}H-NMR ($CDCl_3$) δ : 1.69- 1.91 (8H, m), 2.49 (4H, s), 2.70 (1H, t, J = 12.0 Hz), 2.97 (2H, t, J = 12.0 Hz), 3.12 (2H, s), 4.19 (2H, d, J = 13.0 Hz), 4.76 (2H, s), 6.26 (1H, s), 6.37 (1H, s), 6.82-7.03 (5H, m), 7.16 (2H, dd, J = 5.4, 8.4 Hz).

Melting point: 176 - 178°C (crystallization solvent : ethyl acetate - diisopropyl ether)

Example 143

N-[3-(1-Pyrrolidinylmethyl)-2H-chromen-7-yl][1,1'-

biphenyl]-4-carboxamide



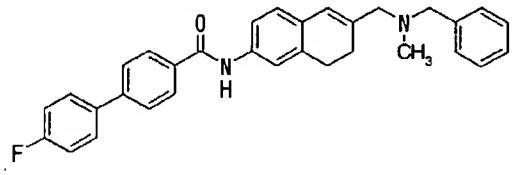
The titled compound was obtained by carrying out the same operation as in Example 1, using 3-(1-pyrrolidinylmethyl)-2H-chromen-7-amine obtained in Reference Example 87.

^{1}H-NMR ($CDCl_3$) δ : 1.79 (4H, s), 2.50 (4H, s), 3.15 (2H, s), 4.81 (2H, s), 6.30 (1H, s), 6.95 (1H, d, J = 8.1 Hz), 7.13 (1H, s), 7.20 (1H, d, J = 8.1 Hz), 7.39-7.50 (3H, m), 7.61-7.70 (4H, m), 7.82 (1H, s), 7.92 (2H, d, J = 8.1 Hz).

Melting point: 198 - 200°C (crystallization solvent : ethyl acetate)

Example 144

N-[6-[(N-Benzyl-N-methylamino)methyl]-7,8-dihydro-2-naphthalenyl]-4'-fluoro[1,1'-biphenyl]-4-carboxamide



The titled compound was obtained by carrying out the same operation as in Example 1, using 6-[(N-benzyl-N-methylamino)methyl]-7,8-dihydro-2-naphthalenamine obtained in Reference Example 88.

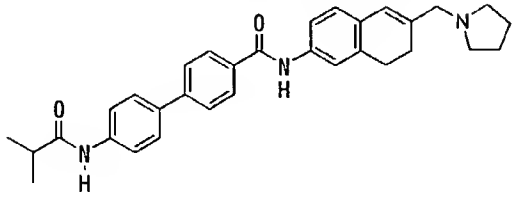
^{1}H-NMR ($CDCl_3$) δ : 2.20 (3H, s), 2.38 (2H, t, J = 8.1 Hz), 2.85 (2H, t, J = 8.1 Hz), 3.09 (2H, s), 3.52 (2H, s), 6.39 (1H, s), 7.02 (1H, d, J = 8.1 Hz), 7.13-7.66 (13H, m), 7.84 (1H, s), 7.93 (2H, d, J = 8.4 Hz).

Melting point: 143 - 145°C (crystallization solvent : ethyl acetate - n-hexane)

Example 145

4'-Isobutyrylamino-N-[6-(1-pyrrolidinylmethyl)-7,8-

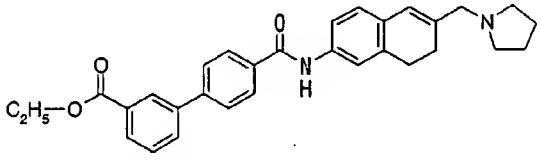
dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained as an amorphous powder by carrying out the same operation as in Example 1, using 6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 54.
MS m/z 494.4 (MH^+).

Example 146

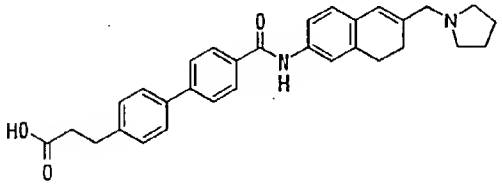
Ethyl 4'-[[[6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl]amino]carbonyl][1,1'-biphenyl]-3-carboxylate



The titled compound was obtained as an amorphous powder by carrying out the same operation as in Example 1, using 6-(1-pyrrolidinylmethyl)-7,8--dihydro-2-naphthalenamine obtained in Reference Example 54.
MS m/z 481.4 (MH^+).

Example 147

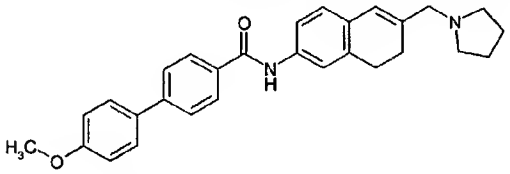
3-[4'-[[[6-(1-Pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl]amino]carbonyl][1,1'-biphenyl]-4-yl]propionic acid



The titled compound was obtained as a powder by carrying out the same operation as in Example 1, using

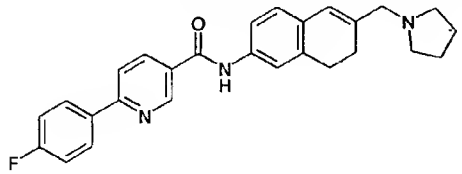
6-(1-pyrrolidinylmethyl)-7,8--dihydro-2-naphthalenamine obtained in Reference Example 54.
MS m/z 481.4 (MH^+).

Example 148
4'-Methoxy-N-[6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained by carrying out the same operation as in Example 1, using 6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 54.
^{1}H-NMR ($CDCl_3$) δ : 1.80 (4H, m), 2.36 (2H, t, J=7.8 Hz), 2.52 (4H, m), 2.86 (2H, t, J=7.8 Hz), 3.18 (2H, s), 3.87 (3H, s), 6.36 (1H, s), 7.00-7.03 (3H, m), 7.26 (1H, m), 7.38 (1H, d, J=8.3 Hz), 7.49 (1H, s), 7.58 (2H, d, J=8.6 Hz), 7.67 (1H, d, J=8.2 Hz), 7.78 (1H, s), 7.90 (2H, d, J=8.2 Hz).
Elemental analysis for $C_{29}H_{30}N_2O_2$
Calcd. : C, 79.42; H, 6.89; N, 6.39.
Found : C, 79.21; H, 6.88; N, 6.35.
Melting point: 187-188 ℃ (crystallization solvent : ethyl acetate - diisopropyl ether)

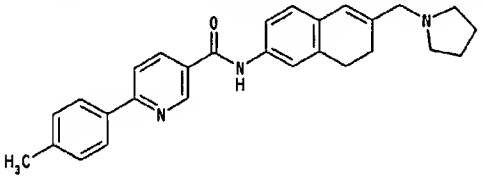
Example 149
6-(4-Fluorophenyl)-N-[6-[(1-pyrrolidinyl)methyl]-7,8-dihydro-2-naphthalenyl]nicotinamide



The titled compound was obtained by carrying out the same operation as in Example 1, using 6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine

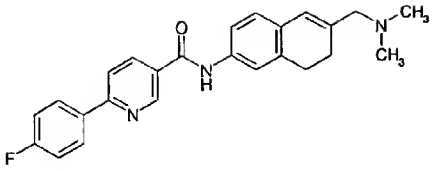
obtained in Reference Example 54.
^{1}H-NMR ($CDCl_3$) δ: 1.81 (4H, m), 2.36 (2H, t, J=8.1 Hz), 2.53 (4H, m), 2.86 (2H, t, J=8.1 Hz), 3.18 (2H, s), 6.37 (1H, s), 7.03 (1H, d, J=7.8 Hz), 7.16-7.30 (3H, m), 7.47 (1H, s), 7.77-7.82 (2H, m), 8.06 (2H, dd, J=8.9, 5.3 Hz), 8.25 (1H, dd, J=8.4, 2.2 Hz), 9.11 (1H, d, J=2.0 Hz).
Elemental analysis for $C_{27}H_{26}FN_3O$
Calcd.: C, 75.85; H, 6.13; N, 9.83.
Found: C, 75.71; H, 5.93; N, 9.75.
Melting point: 225-227 ℃ (crystallization solvent: ethyl acetate - diisopropyl ether)

Example 150
6-(4-Methylphenyl)-N-[6-[(1-pyrrolidinyl)methyl]-7,8-dihydro-2-naphthalenyl]nicotinamide



The titled compound was obtained by carrying out the same operation as in Example 1, using 6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 54.
^{1}H-NMR ($CDCl_3$) δ: 1.81 (4H, m), 2.36 (2H, t, J=7.8 Hz), 2.43 (3H, s), 2.53 (4H, m), 2.86 (2H, t, J=7.8 Hz), 3.19 (2H, s), 6.37 (1H, s), 7.02 (1H, d, J=8.7 Hz), 7.25-7.39 (3H, m), 7.47 (1H, s), 7.82 (2H, m), 7.96 (2H, d, J=8.1 Hz), 8.23 (1H, dd, J=8.1, 2.3 Hz), 9.12 (1H, d, J=2.3 Hz).
Melting point: 235-236 ℃ (crystallization solvent: ethyl acetate - diisopropyl ether)

Example 151
N-[6-[(Dimethylamino)methyl]-7,8-dihydro-2-naphthalenyl]-6-(4-fluorophenoxy)nicotinamide



The titled compound was obtained by carrying out the same operation as in Example 1, using 6-[(N,N-dimethylamino)methyl]-7,8-dihydro-2-naphthalenamine obtained in Reference Example 41-2).

^{1}H-NMR ($CDCl_3$) δ: 2.25 (6H, s), 2.34 (2H, t, J=8.1 Hz), 2.86 (2H, t, J=8.1 Hz), 2.99 (2H, s), 6.35 (1H, s), 7.03 (1H, d, J=8.1 Hz), 7.17 (2H, m), 7.26 (1H, m), 7.39 (1H, d, J=8.1 Hz), 7.47 (1H, s), 7.78 (1H, d, J=7.2 Hz), 7.83 (1H, s), 8.06 (1H, dd, J=8.4, 6.7 Hz), 8.25 (1H, d, J=6.7 Hz), 9.12 (1H, s).

Elemental analysis for $C_{25}H_{24}FN_3O$

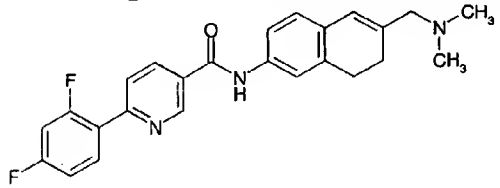
Calcd.: C, 74.79; H, 6.03; N, 10.47.

Found: C, 74.74; H, 5.95; N, 10.24.

Melting point: 216-219 ℃ (crystallization solvent: ethyl acetate - diisopropyl ether)

Example 152

6-(2,4-Difluorophenyl)-N-[6-[(dimethylamino)methyl]-7,8-dihydro-2-naphthalenyl]nicotinamide



The titled compound was obtained by carrying out the same operation as in Example 1, using 6-[(N,N-dimethylamino)methyl]-7,8-dihydro-2-naphthalenamine obtained in Reference Example 41-2).

^{1}H-NMR ($CDCl_3$) δ: 2.25 (6H, s), 2.34 (2H, t, J=8.1 Hz), 2.85 (2H, t, J=8.1 Hz), 3.00 (2H, s), 6.35 (1H, s), 6.90-7.06 (3H, m), 7.39 (1H, d, J=7.8 Hz), 7.47 (1H, s), 7.80-7.90 (2H, m), 8.10 (1H, dd, J=15.3, 8.8 Hz), 8.23 (1H, dd, J=8.4, 2.3 Hz), 9.15 (1H, d, J=1.7 Hz).

Elemental analysis for $C_{25}H_{23}F_2N_3O$

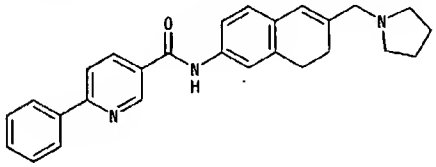
Calcd. : C, 71.58; H, 5.53; N, 10.02.

Found : C, 71.50; H, 5.49; N, 9.61.

Melting point: 162-163 ℃ (crystallization solvent : ethyl acetate - diisopropyl ether)

Example 153

6-Phenyl-N-[6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl]nicotinamide



The titled compound was obtained by carrying out the same operation as in Example 1, using 6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 54.

^{1}H-NMR ($CDCl_3$) δ : 1.81 (4H, m), 2.36 (2H, t, J=8.1 Hz), 2.53 (4H, m), 2.85 (2H, t, J=8.1 Hz), 3.18 (2H, s), 6.37 (1H, s), 7.02 (1H, d, J=8.1 Hz), 7.37-7.53 (5H, m), 7.83 (1H, d, J=8.1 Hz), 7.86 (1H, d, J=6.2 Hz), 8.04 (1H, s), 8.06 (1H, d, J=1.7 Hz), 8.24 (1H, dd, J=8.4, 2.4 Hz), 9.13 (1H, d, J=2.2 Hz).

Elemental analysis for $C_{27}H_{27}N_3O$

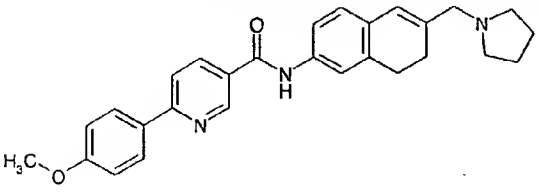
Calcd. : C, 79.19; H, 6.65; N, 10.26.

Found : C, 78.93; H, 6.65; N, 10.19.

Melting point: 186-187 ℃ (crystallization solvent : ethyl acetate - diisopropyl ether)

Example 154

6-(4-Methoxyphenyl)-N-[6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl]nicotinamide



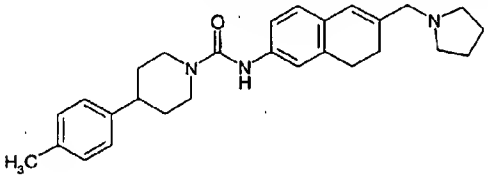
The titled compound was obtained by carrying out the same operation as in Example 1, using 6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 54.

^{1}H-NMR ($CDCl_3$) δ : 1.80 (4H, m), 2.36 (2H, t, J=8.1 Hz), 2.52 (4H, m), 2.84 (2H, t, J=8.1 Hz), 3.18 (2H, s), 3.88 (3H, s), 6.36 (1H, s), 7.02 (3H, m), 7.37 (1H, d, J=7.5 Hz), 7.47 (1H, s), 7.78 (1H, d, J=8.1 Hz), 7.79 (1H, s), 8.03 (2H, d, J=8.5 Hz), 8.20 (1H, d, J=8.1 Hz), 9.08 (1H, s).

Melting point: 219-220 ℃ (crystallization solvent: ethyl acetate - diisopropyl ether)

Example 155

4-(4-Methylphenyl)-N-[6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl]-1-piperidinecarboxamide



The titled compound was obtained by carrying out the same operation as in Example 99, using 6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 54.

^{1}H-NMR ($CDCl_3$) δ : 1.64-1.92 (8H, m), 2.29 (2H, m), 2.32 (3H, s), 2.51 (4H, m), 2.64 (1H, m), 2.80 (2H, t, J=7.8 Hz), 2.97 (2H, dd, J=13.1, 10.7 Hz), 3.15 (2H, s), 4.19 (2H, d, J=13.1 Hz), 6.32 (1H, s), 6.35 (1H, s), 6.42 (1H, d, J=7.8 Hz), 7.06-7.20 (6H, m)

Elemental analysis for $C_{28}H_{35}N_3O \cdot 0.5H_2O$

Calcd. : C, 76.67; H, 8.27; N, 9.58.

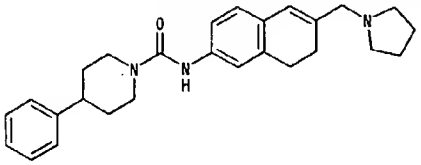
Found : C, 76.72; H, 8.03; N, 9.36.

Melting point: 197-198 ℃ (crystallization solvent : ethyl acetate - diisopropyl ether)

Example 156

4-Phenyl-N-[6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-

naphthalenyl]-1-piperidinecarboxamide



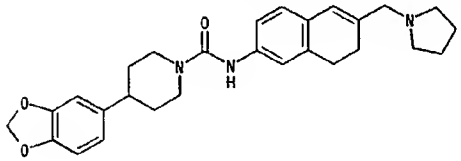
The titled compound was obtained by carrying out the same operation as in Example 99, using 6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 54.

^{1}H-NMR ($CDCl_3$) δ : 1.72-1.94 (8H, m), 2.32 (2H, t, J=8.1 Hz), 2.50 (4H, m), 2.72 (1H, m), 2.80 (2H, t, J=8.1 Hz), 2.99 (2H, dd, J=13.4, 10.6 Hz), 3.16 (2H, s), 4.21 (2H, d, J=13.4 Hz), 6.32 (1H, s), 6.34 (1H, s), 6.93 (1H, d, J=8.4 Hz), 7.07 (1H, d, J=8.1 Hz), 7.20-7.35 (6H, m).

Melting point: 184-186 ℃ (crystallization solvent : ethyl acetate - diisopropyl ether)

Example 157

4-(1,3-Benzodioxol-5-yl)-N-[6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl]-1-piperidinecarboxamide



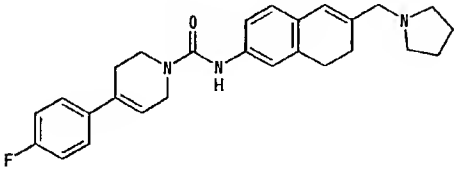
The titled compound was obtained by carrying out the same operation as in Example 99, using 6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 54.

^{1}H-NMR ($CDCl_3$) δ : 1.61-1.88 (8H, m), 2.31 (2H, t, J=8.1 Hz), 2.51 (4H, m), 2.59 (1H, m), 2.62 (2H, t, J=8.1 Hz), 2.94 (2H, dd, J=13.1, 11.2 Hz), 3.15 (2H, s), 4.18 (2H, d, J=13.1 Hz), 5.93 (2H, s), 6.31 (1H, s), 6.44 (1H, s), 6.64-6.77 (3H, m), 6.92 (1H, d, J=8.1 Hz), 7.07 (1H, d, J=8.1 Hz), 7.19 (1H, s).

Melting point: 149-150 ℃ (crystallization solvent : ethyl acetate - diisopropyl ether)

Example 158

4-(4-Fluorophenyl)-N-[6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl]-3,6-dihydro-1(2H)-pyridinecarboxamide



The titled compound was obtained by carrying out the same operation as in Example 99, using 6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 54.

^{1}H-NMR ($CDCl_3$) δ : 1.79 (4H, m), 2.32 (2H, t, J=8.1 Hz), 2.50 (4H, m), 2.59 (2H, brt), 2.80 (2H, t, J=8.1 Hz), 3.17 (2H, s), 3.74 (2H, t, J=5.7 Hz), 4.15 (2H, d, J=2.5 Hz), 6.00 (1H, brt), 6.32 (1H, s), 6.32 (1H, s), 6.94 (1H, d, J=8.1 Hz), 7.00-7.32 (6H, m).

Elemental analysis for $C_{27}H_{30}FN_3O$

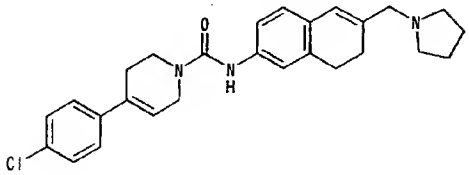
Calcd. : C, 75.15; H, 7.01; N, 9.74.

Found : C, 75.09; H, 6.93; N, 9.77.

Melting point: 206-207 ℃ (crystallization solvent : ethyl acetate - diisopropyl ether)

Example 159

4-(4-Chlorophenyl)-N-[6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl]-3,6-dihydro-1(2H)-pyridinecarboxamide



The titled compound was obtained by carrying out the same operation as in Example 99, using 6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 54.

^{1}H-NMR ($CDCl_3$) δ : 1.79 (4H, m), 2.32 (2H, t, J=8.1 Hz), 2.50 (4H, m), 2.59 (2H, brt), 2.80 (2H, t, J=8.1 Hz), 3.16 (2H, s), 3.73 (2H, t, J=5.6 Hz), 4.15 (2H, d, J=2.8 Hz), 6.06 (1H, brt), 6.30 (1H, s), 6.32 (1H, s), 6.93 (1H, d, J=7.8 Hz), 7.09 (1H, d, J=7.8 Hz), 7.21-7.31 (5H, m).

Elemental analysis for $C_{27}H_{30}ClN_3O$

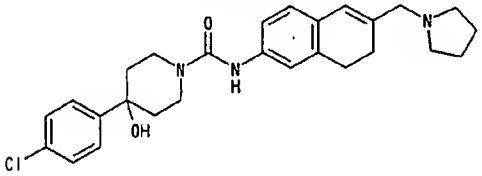
Calcd. : C, 72.39; H, 6.75; N, 9.38.

Found : C, 72.19; H, 6.75; N, 9.19.

Melting point: 217-218 ℃ (crystallization solvent : ethyl acetate - diisopropyl ether)

Example 160

4-(4-Chlorophenyl)-4-hydroxy-N-[6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl]-1-piperidinecarboxamide



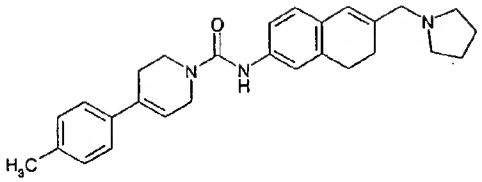
The titled compound was obtained by carrying out the same operation as in Example 99, using 6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 54.

^{1}H-NMR ($CDCl_3$) δ : 1.79 (4H, m), 1.80 (2H, m), 2.04 (1H, dd, J=13.1, 10.8 Hz), 2.06 (1H, dd, J=13.1, 10.8 Hz), 2.31 (2H, t, J=7.8 Hz), 2.50 (1H, brs), 2.51 (4H,m), 2.79 (2H, t, J=7.8 Hz), 3.15 (2H, s), 3.41 (2H, dd, J=12.6, 10.8 Hz), 4.00 (2H, d, J=12.6 Hz), 6.32 (1H, s), 6.37 (1H, s), 6.93 (1H, d, J=8.1 Hz), 7.05-7.42 (6H, m).

Melting point: 181-182 ℃ (crystallization solvent : ethyl acetate - diisopropyl ether)

Example 161

4-(4-Methylphenyl)-N-[6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl]-3,6-dihydro-1(2H)-pyridinecarboxamide



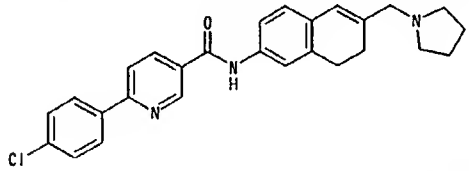
The titled compound was obtained by carrying out the same operation as in Example 99, using 6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 54.

^{1}H-NMR ($CDCl_3$) δ: 1.79 (4H, m), 2.32 (2H, t, J=7.8 Hz), 2.35 (3H, s), 2.50 (4H, m), 2.61 (2H, brt), 2.80 (2H, t, J=7.8 Hz), 3.16 (2H, s), 3.73 (2H, t, J=5.7 Hz), 4.15 (2H, d, J=2.8 Hz), 6.03 (1H, s), 6.29 (1H, s), 6.32 (1H, s), 6.93 (1H, d, J=8.1 Hz), 7.07-7.30 (6H, m).

Melting point: 199-202 ℃ (crystallization solvent: ethyl acetate - diisopropyl ether)

Example 162

6-(4-Chlorophenyl)-N-[6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl]nicotinamide



The titled compound was obtained by carrying out the same operation as in Example 1, using 6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 54.

^{1}H-NMR ($CDCl_3$+DMSO-d_6) δ: 1.80 (4H, m), 2.32-2.58 (6H, m), 2.85 (2H, t, J=8.0 Hz), 3.18 (2H, s), 6.36 (1H, s), 7.01 (1H, d, J=8.4 Hz), 7.48 (2H, d, J=8.4 Hz), 7.49 (1H, m), 7.59 (1H, s), 7.83 (1H, d, J=8.4 Hz), 8.04 (2H, d, J=8.4 Hz), 8.35 (1H, dd, J=8.4, 2.2 Hz), 9.25 (1H, d, J=2.2 Hz), 9.42 (1H, s).

Elemental analysis for $C_{27}H_{26}ClN_3O$

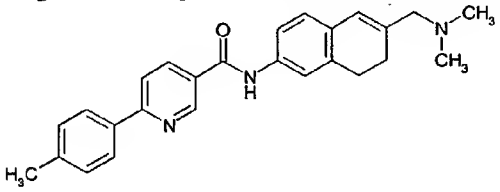
Calcd.: C, 73.04; H, 5.90; N, 9.46.

Found: C, 73.11; H, 5.71; N, 9.20.

Melting point: 252-253 ℃ (crystallization solvent: ethyl acetate - diisopropyl ether)

Example 163

N-[6-[(Dimethylamino)methyl]-7,8-dihydro-2-naphthalenyl]-6-(4-methylphenyl)nicotinamide



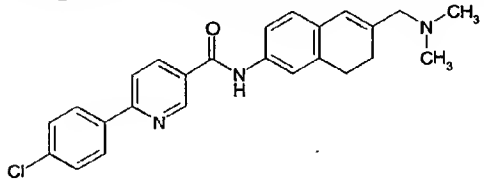
The titled compound was obtained by carrying out the same operation as in Example 1, using 6-[(N,N-dimethylamino)methyl]-7,8-dihydro-2-naphthalenamine obtained in Reference Example 41-2).

^{1}H-NMR ($CDCl_3$) δ: 2.25 (6H, s), 2.34 (2H, t, J=8.1 Hz), 2.43 (3H, s), 2.85 (2H, t, J=8.1 Hz), 2.99 (2H, s), 6.34 (1H, s), 7.02 (1H, d, J=8.1 Hz), 7.31 (2H, d, J=8.1 Hz), 7.39 (1H, d, J=8.1 Hz), 7.46 (1H, s), 7.81 (1H, d, J=8.4 Hz), 7.87 (1H, s), 7.96 (2H, d, J=8.1 Hz), 8.22 (1H, dd, J=8.4, 2.3 Hz), 9.11 (1H, d, J=2.3 Hz).

Melting point: 228-230 ℃ (crystallization solvent: ethyl acetate - diisopropyl ether)

Example 164

6-(4-Chlorophenyl)-N-[6-[(dimethylamino)methyl]-7,8-dihydro-2-naphthalenyl]nicotinamide



The titled compound was obtained by carrying out the same operation as in Example 1, using 6-[(N,N-dimethylamino)methyl]-7,8-dihydro-2-naphthalenamine obtained in Reference Example 41-2).

^{1}H-NMR ($CDCl_3$) δ: 2.25 (6H, s), 2.35 (2H, t, J=8.1 Hz), 2.86 (2H, t, J=8.1 Hz), 2.99 (2H, s), 6.35 (1H, s), 7.04 (1H,

d, J=8.1 Hz), 7.40 (1H, d, J=8.4 Hz), 7.49 (1H, brs), 7.49 (2H, d, J=8.4 Hz), 7.78 (1H, s), 7.84 (1H, d, J=8.4 Hz), 8.02 (2H, d, J=8.4 Hz), 8.26 (1H, dd, J=8.1, 2.2 Hz), 9.13 (1H, d, J=2.2 Hz).

Elemental analysis for $C_{25}H_{24}ClN_3O$

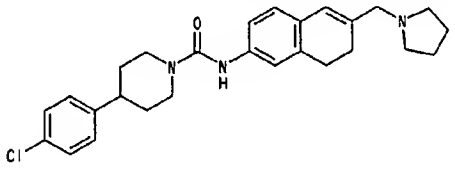
Calcd.: C, 71.85; H, 5.79; N, 10.05.

Found: C, 71.88; H, 5.67; N, 9.86.

Melting point: 248-249 ℃ (crystallization solvent: ethyl acetate - diisopropyl ether)

Example 165

4-(4-Chlorophenyl)-N-[6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl]-1-piperidinecarboxamide



The titled compound was obtained by carrying out the same operation as in Example 99, using 6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 54.

^{1}H-NMR ($CDCl_3$) δ: 1.66-1.91 (8H, m), 2.32 (2H, t, J=8.1 Hz), 2.50 (4H, m), 2.70 (1H, m), 2.80 (2H, t, J=8.1 Hz), 2.98 (2H, dd, J=13.7, 12.0 Hz), 3.16 (2H, s), 4.20 (2H, d, J=13.7 Hz), 6.32 (1H, s), 6.32 (1H, s), 6.93 (1H, d, J=8.1 Hz), 7.05-7.30 (6H, m).

Elemental analysis for $C_{27}H_{32}ClN_3O$

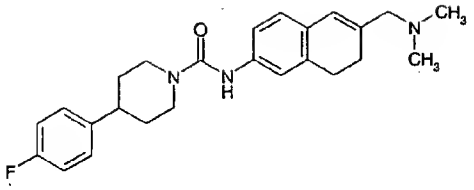
Calcd.: C, 72.06; H, 7.17; N, 9.34.

Found: C, 72.08; H, 7.23; N, 9.15.

Melting point: 194-195 ℃ (crystallization solvent: ethyl acetate - diisopropyl ether)

Example 166

N-[6-[(Dimethylamino)methyl]-7,8-dihydro-2-naphthalenyl]-4-(4-fluorophenyl)-1-piperidinecarboxamide



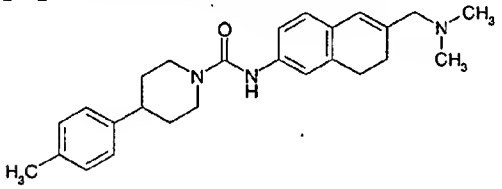
The titled compound was obtained by carrying out the same operation as in Example 99, using 6-[(N,N-dimethylamino)methyl]-7,8-dihydro-2-naphthalenamine obtained in Reference Example 41-2).

^{1}H-NMR ($CDCl_3$) δ: 1.65-1.75 (2H, m), 1.89 (2H, d, J=11.4 Hz), 2.23 (6H, s), 2.30 (2H, t, J=8.1 Hz), 2.70 (1H, m), 2.80 (2H, t, J=8.1 Hz), 2.94-3.01 (4H, m), 4.20 (2H, d, J=13.4 Hz), 6.30 (1H, s), 6.35 (1H, s), 6.92-7.20 (7H, m).

Melting point: 187-188 ℃ (crystallization solvent: ethyl acetate - diisopropyl ether)

Example 167

N-[6-[(Dimethylamino)methyl]-7,8-dihydro-2-naphthalenyl]-4-(4-methylphenyl)-1-piperidinecarboxamide



The titled compound was obtained by carrying out the same operation as in Example 99, using 6-[(N,N-dimethylamino)methyl]-7,8-dihydro-2-naphthalenamine obtained in Reference Example 41-2).

^{1}H-NMR ($CDCl_3$) δ: 1.66-1.74 (2H, m), 1.89 (2H, d, J=11.7 Hz), 2.28 (6H, s), 2.30 (2H, t, J=8.1 Hz), 2.38 (3H, s), 2.68 (1H, m), 2.80 (2H, t, J=8.1 Hz), 2.94-3.02 (4H, m), 4.19 (2H, d, J=12.8 Hz), 6.30 (1H, s), 6.35 (1H, s), 6.93 (1H, d, J=8.1 Hz), 7.07-7.20 (6H, m).

Elemental analysis for $C_{26}H_{33}N_3O \cdot 0.5H_2O$

Calcd.: C, 75.69; H, 8.31; N, 10.18

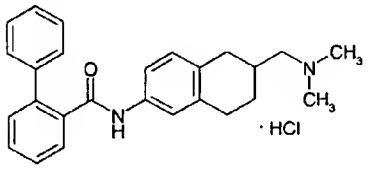
Found: C, 75.44; H, 8.16; N, 10.05

Melting point: 200-202 ℃ (crystallization solvent: ethyl

acetate - diisopropyl ether)

Example 168

N-[6-[(Dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl][1,1'-biphenyl]-2-carboxamide hydrochloride



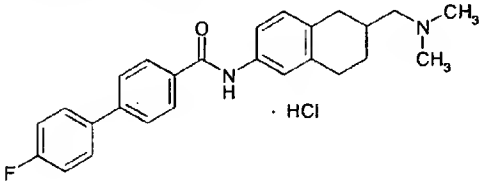
The titled compound was obtained by carrying out the same operation as in Example 1, using 6-amino-2-[(N,N-dimethylamino)methyl]tetralin hydrochloride.

^{1}H-NMR (DMSO-d_6) δ: 1.39 (1H, m), 1.99 (1H, m), 2,17 (1H, m), 2.42 (1H, dd, J=16.2, 10.1 Hz), 2.78 (6H, s), 2.88 (1H, dd, J=16.2, 4.5 Hz), 3.06 (2H, t, J=5.7 Hz), 3.38 (2H, s), 6.94-7.62 (11H, m), 7.64 (1H, d, J=1.7 Hz), 10.11 (1H, brs), 10.18 (1H,s).

Melting point: 196-197 ℃ (crystallization solvent: methanol - ethyl acetate)

Example 169

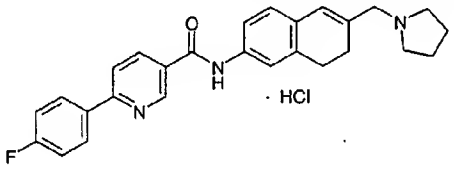
N-[6-[(Dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]-4'-fluoro[1,1'-biphenyl]-4-carboxamide hydrochloride



4'-Fluoro-N -[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide synthesized in Example 42 was dissolved in ethyl acetate. An excess amount of 4N hydrochloric acid-ethyl acetate solution was added to the solution, which was concentrated under reduced pressure. The resulting residue was recrystallized from methanol - ethyl

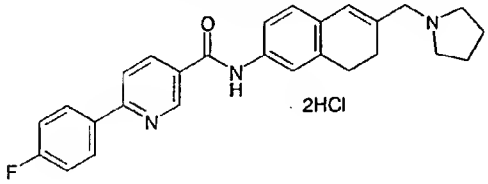
acetate, to give the titled compound.
^{1}H-NMR (DMSO-d_6) δ: 1.43 (1H, m), 2.06 (1H, m), 2.21 (1H, m), 2.45 (1H, m), 2.79 (6H, s), 2.92 (1H, dd, J=16.2, 4.2 Hz), 3.08 (2H, d, J=6.4 Hz), 3.33 (2H, s), 7.05 (1H, d, J=8.4 Hz), 7.34 (2H, dd, J=8.9, 8.9 Hz), 7.53 (1H, d, J=8.4 Hz), 7.59 (1H, s), 7.80 (4H, m), 8.06 (2H, d, J=8.1 Hz), 10.02 (1H, s), 10.03 (1H, brs).
Melting point: 240-245 ℃ (crystallization solvent: methanol - ethyl acetate)

Example 170
6-(4-Fluorophenyl)-N-[6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl]nicotinamide hydrochloride



The titled compound was obtained by carrying out the same operation as in Example 1, using 6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 54.
^{1}H-NMR (DMSO-d_6) δ: 1.70 (4H, m), 2.26 (2H, t, J=8.1 Hz), 2.44 (4H, m), 2.76 (2H, t, J=8.1 Hz), 3.12 (2H, s), 3.34 (1H, s), 6.36 (1H, s), 7.03 (1H, d, J=7.8 Hz), 7.37 (2H, dd, J=8.4, 7.0 Hz), 7.57 (1H, d, J=8.4 Hz), 7.59 (1H, s), 8.13-8.42 (4H, m), 9.19 (1H, s), 10.43 (1H,s).
Melting point: 229-231 ℃ (crystallization solvent: methanol - ethyl acetate)

Example 171
6-(4-Fluorophenyl)-N-[6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl]nicotinamide dihydrochloride



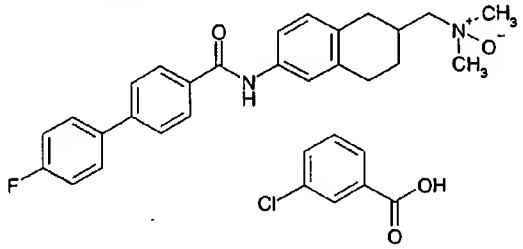
The titled compound was obtained by carrying out the same operation as in Example 1, using 6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 54.

^{1}H-NMR (DMSO-d_6) δ: 2.00 (4H, m), 2.45 (4H, m), 2.83 (2H, t, J=8.1 Hz), 3.05 (2H, m), 3.47 (2H, m), 3.88 (1H, s), 6.69 (1H, s), 7.13 (1H, d, J=8.1 Hz), 7.38 (2H, dd, J=8.9, 8.6 Hz), 7.64 (1H, d, J=10.6 Hz), 7.66 (1H, s), 8.14-8.42 (4H, m), 9.19 (1H, s), 10.52 (1H, s), 10.60 (1H,brs).

Melting point: 245-248 ℃ (crystallization solvent : methanol - ethyl acetate)

Example 172

N-[6-[(Dimethylnitroyl)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]-4'-fluoro[1,1'-biphenyl]-4-carboxamide 3-chlorobenzoate



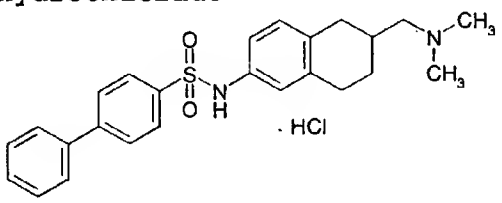
4'-FluoroN-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide (100 mg) obtained in Example 42 was dissolved in acetone (10 ml), which was stirred under ice-cooling. 3-Chloroperbenzoic acid (purity : 50%) (86 mg) was added to the solution, which was stirred under ice-cooling for 1 hour. The reaction mixture was concentrated under reduced pressure, and the residue was washed with diisopropyl ether, to give the titled compound (158 mg).

^{1}H-NMR (DMSO-d_6) δ: 1.57 (1H, m), 2.07 (1H, m), 2.61 (1H, m), 2.82 (2H, m), 3.04 (1H, m), 3.33 (1H, m), 3.48 (6H, s), 3.56-3.67 (2H, m), 6.55 (1H, s), 7.03 (1H, d, J=8.4 Hz), 7.30-7.56 (6H, m), 7.78-7.85 (6H, m), 8.04 (2H, d, J=8.4 Hz), 10.17 (1H, s).

FABMS(pos) 419.1 [M+H]+

Example 173

N-[6-[(Dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl][1,1'-biphenyl]-4-sulfonamide hydrochloride



6-[(N, N-Dimethylamino)methyl]-7,8-dihydro-2-naphthalenamine (200 mg, 0.72 mmol) obtained in Example 41-2) was dissolved in acetonitrile (30 ml). Triethylamine (0.401 ml, 2.88 mmol) and [1,1'-biphenyl]-4-sulfonylchloride (200 mg, 0.79 mmol) were added to the solution under ice-cooling, which was stirred for 3 hours. The reaction mixture was concentrated. Ethyl acetate and water were added to the residue, and extraction was conducted. The ethyl acetate layer was concentrated, and the residue was purified by alumina column chromatography (development solvent ; ethyl acetate:n-hexane = 33:67). 4N Hydrogen chloride-ethyl acetate solution was added to the resulting oily substance, which was concentrated. The residue was recrystallized from methanol - ethyl acetate, to give the titled compound (194 mg).

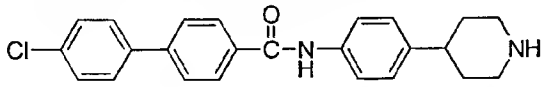
^{1}H-NMR (DMSO-d_6) δ : 1.32 (1H, m), 1.96 (1H, m), 2.11 (1H, m), 2.35 (1H, d, J=15.9, 10.0 Hz), 2.74 (2H, m), 2.78 (7H, m), 3.02 (2H, m), 6.89 (2H, d, J=10.6 Hz), 6.91 (1H, m), 7.40-7.51 (3H, m), 7.70 (2H, d, J=6.7 Hz), 7.85 (4H, m), 9.92 (1H, brs), 10.23 (1H, s).

Melting point: 168-170 ℃ (crystallization solvent : methanol - ethyl acetate)

FABMS(pos) 421.1 [M+H]+

Example 174

4'-Chloro-N -[4-(4-piperidininyl)phenyl][1,1'-biphenyl]-4-carboxamide



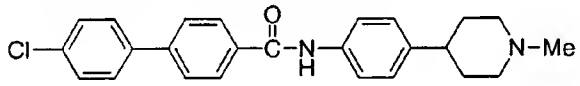
The titled compound was obtained as a colorless powder by carrying out the same operation as in Example 127-2), using 4'-chloro-N-[4-(4-piperidininyl)phenyl][1,1'-biphenyl]-4-carboxamide obtained in Reference Example 89.

^{1}H-NMR ($CDCl_3$+ DMSO-d_6) δ: 1.40-1.90 (4H, m), 2.60-2.90 (3H, m), 3.18-3.28 (2H, m), 7.19 (2H, d, J=8.1 Hz), 7.49 (2H, d, J=7.0 Hz), 7.67-7.75 (6H, m), 8.07-8.10 (3H, m), 10.16 (1H, s).

Melting point: 276-281 ℃ (decomposition) (crystallization solvent : ethyl acetate)

Example 175

4'-Chloro-N -[4-(1-methyl4-piperidininyl)phenyl][1,1'-biphenyl]-4-carboxamide

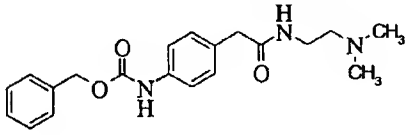


A mixture of 4'-chloro-N-[4-(4-piperidininyl)phenyl][1,1'-biphenyl]-4-carboxamide (0.17 g) obtained in Example 174, 37% aqueous formaldehyde solution (0.05 ml) and formic acid (0.5 ml) was heated at 100℃ for 4 hours. The reaction mixture was cooled to room temperature. Water was added to the mixture, which was made alkaline with 8N aqueous sodium hydroxide solution, and extracted with ethyl acetate - tetrahydrofuran (1:1) mixed solution. The extract was washed with saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, and then the solvent was distilled out under reduced pressure. The resulting solid was washed with ethyl acetate, dried under reduced pressure, to give the titled compound (90 mg).

^{1}H-NMR ($CDCl_3$+ DMSO-d_6) δ: 1.55-1.80 (2H, m), 1.90-2.10

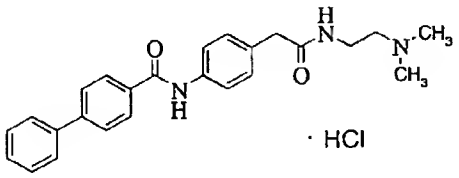
(2H, m), 2.22 (3H, s), 2.30-2.45 (1H, m), 2.80-3.20 (4H, m), 7.11 (2H, d, J=8.1 Hz), 7.36 (2H, d, J=8.1 Hz), 7.50-7.63 (6H, m), 7.97 (2H, d, J=8.4 Hz), 9.79 (1H, s).
Melting point: 273-277 ℃ (decomposition) (Washing solvent : ethyl acetate)

Example 176
Benzyl 4-[2-[[2-(dimethylamino)ethyl]amino]-2-oxoethyl]phenylcarbamate



N,N-Dimethylethylenediamine (0.64 ml), WSC (1.31 g), HOBt (1.05 g), and triethylamine (2.4 ml) were added to a tetrahydrofuran (50 ml) solution of 2-[4-[[(benzyloxy)carbonyl]amino]phenyl]acetic acid (1.5 g) obtained in Reference Example 90. After stirring for 20 hours, the reaction mixture was poured into water, and extraction was conducted using ethyl acetate. The organic layer was washed with water, saturated aqueous sodium bicarbonate solution, and saturated aqueous sodium chloride solution, dried and then concentrated. The residue was recrystallized from ethyl acetate - hexane, to give the titled compound (1.72 g).
Melting point: 126-127 ℃.

Example 177
N-[4-[2-[[2-(Dimethylamino)ethyl]amino]-2-oxoethyl]phenyl][1,1'-biphenyl]-4-carboxamide hydrochloride



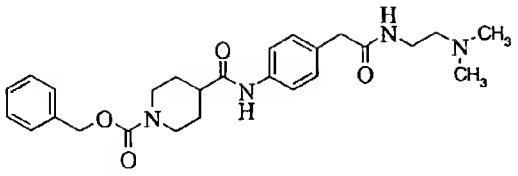
Oxalyl chloride (0.56 ml) was added dropwise to a

tetrahydrofuran (45 ml) solution of 4-biphenylcarboxylic acid (1.01 g) under ice-cooling. 9 drops of DMF was added to the mixture, and the temperature of the mixture was raised to room temperature, which was stirred for 40 minutes. The reaction mixture was concentrated and dried. A tetrahydrofuran (50 ml) solution of the residue was added dropwise to a tetrahydrofuran (45 ml) solution of 2-(4-aminophenyl)-N-[2-(dimethylamino)ethyl]acetamide (939 mg) obtained in Reference Example 91 under ice-cooling. Then the temperature of the reaction mixture was raised to room temperature, which was stirred for 2 hours. Saturated aqueous sodium bicarbonate solution was added to the reaction mixture, and extraction was conducted using ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride solution, dried over sodium sulfate, and then concentrated. The residue was dissolved in tetrahydrofuran. 4N Hydrochloric acid-ethyl acetate was added to the solution, which was concentrated. The residue was recrystallized from methanol - diisopropyl ether, to give the titled compound (750 mg).
Melting point: 216-217 ℃.

The above N-[4-[2-[[2-(dimethylamino)ethyl]amino]-2-oxoethyl]phenyl][1,1'-biphenyl]-4-carboxyamide hydrochloride (100 mg) was dissolved in saturated aqueous sodium bicarbonate solution, and extraction was conducted using tetrahydrofuran-ethyl acetate (1:1). The organic layer was washed with saturated aqueous sodium chloride solution, dried over sodium sulfate, and then concentrated. The residue was recrystallized from methanol - diisopropyl ether, to give a free base form (56 mg) of the titled compound.
Melting point: 228-229 ℃.

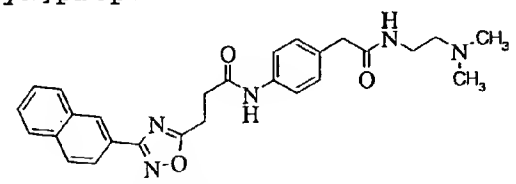
Example 178

Benzyl 4-[[4-[2-[[2-(dimethylamino)ethyl]amino]-2-oxoethyl]anilino]carbonyl]-1-piperidinecarboxylate



2-(4-Aminophenyl)-N-[2-(dimethylamino)ethyl]acetamide (221 mg), WSC (249 mg), 1-hydroxybenzotriazole (199 mg), triethylamine (0.4 ml), and dimethylaminopyridine (244 mg) were added to a tetrahydrofuran (10 ml) solution of 1-[(benzyloxy)carbonyl]-4-piperidinecarboxylic acid (290 mg), which was stirred for 20 hours. The reaction mixture was poured into water, and extraction was conducted using ethyl acetate. The organic layer was washed with water, saturated aqueous sodium bicarbonate solution, and saturated aqueous sodium chloride solution, dried over sodium sulfate, and then concentrated. The residue was recrystallized from methanol - diisopropyl ether, to give the titled compound (230 mg).
Melting point: 169-170 ℃.

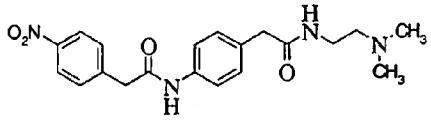
Example 179
N-[4-[2-[[2-(Dimethylamino)ethyl]amino]-2-oxoethyl]phenyl]-3-[3-(2-naphthyl)-1,2,4-oxadiazol-5-yl]propanamide



2-(4-Aminophenyl)-N-[2-(dimethylamino)ethyl]acetamide (221 mg), WSC (249 mg), 1-hydroxybenzotrizole (199 mg), triethylamine (0.4 ml), and dimethylaminopyridine (244 mg) were added to a DMF (5 ml) solution of 3-[3-(2-naphthyl)-1,2,4-oxadiazol-5-yl]propionic acid (268 mg), which was stirred for 5 hours. The reaction mixture was poured into water, and extraction was conducted using ethyl acetate. The organic layer was

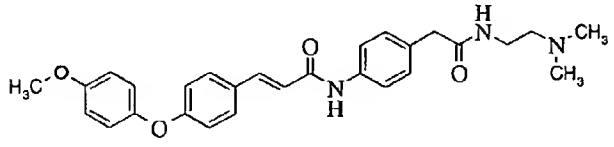
washed with water, saturated aqueous sodium bicarbonate solution, and saturated aqueous sodium chloride solution, dried over sodium sulfate, and then concentrated. The residue was recrystallized from methanol, to give the titled compound (166 mg).
Melting point: 173-174 ℃.

Example 180
N-[4-[2-[[2-(Dimethylamino)ethyl]amino]-2-oxoethyl]phenyl]-2-(4-nitrophenyl)acetamide



2-(4-Aminophenyl)-N-[2-(dimethylamino)ethyl]acetamide (221 mg), WSC (free form : 0.23 ml), 1-hydroxybenzotriazole (199 mg), and dimethylaminopyridine (244 mg) were added to a DMF (5 ml) solution of 4-nitrophenylacetic acid (181 mg), which was stirred for 4 hours. The reaction mixture was poured into water, and extraction was conducted using ethyl acetate. The organic layer was washed with water, saturated aqueous sodium bicarbonate solution, and saturated aqueous sodium chloride solution, dried over sodium sulfate, and then concentrated. The residue was recrystallized from methanol, to give the titled compound (80 mg).
Melting point: 160-162 ℃.

Example 181
(E)-N-[4-[2-[[2-(Dimethylamino)ethyl]amino]-2-oxoethyl]phenyl]-3-[4-(4-methoxyphenoxy)phenyl]-2-propanamide

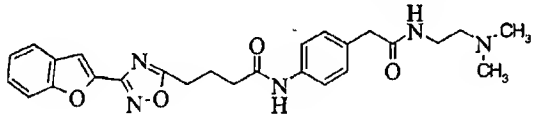


2-(4-Aminophenyl)-N-[2-(dimethylamino)ethyl]acetamide (221 mg), WSC (free form :

0.23 ml), 1-hydroxybenzotriazole (199 mg), triethylamine (0.14 ml) and dimethylaminopyridine (122 mg) were added to a DMF (5 ml) solution of (E)-3-[4-(4-methoxyphenoxy)phenyl]-2-propenoic acid (270 mg), which was stirred for 24 hours. The reaction mixture was poured into water, and extraction was conducted using ethyl acetate - tetrahydrofuran (1:1). The organic layer was washed with water, saturated aqueous sodium bicarbonate solution, and saturated aqueous sodium chloride solution, dried over sodium sulfate, and then concentrated. The resulting crude crystals were washed with diisopropyl ether, to give the titled compound (227 mg).
Melting point: 175-177 ℃ (decomposition).

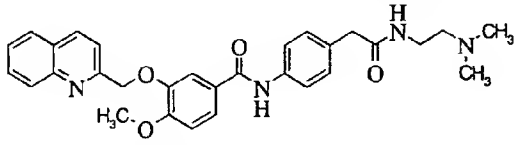
Compounds described in the following Example 182 to 198 were produced in the same manner as in Example 181.

Example 182
4-[3-(1-Benzofuran-2-yl)-1,2,4-oxadiazol-5-yl]-N-[4-[2-[[2-(dimethylamino)ethyl]amino]-2-oxoethyl]phenyl]butanamide



Melting point: 161-163 ℃.
Washing solvent : diisopropyl ether.

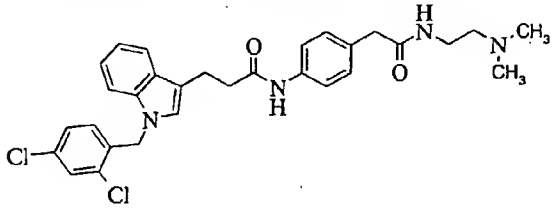
Example 183
N-[4-[2-[[2-(Dimethylamino)ethyl]amino]-2-oxoethyl]phenyl]-3-methoxy-4-(2-quinolinylmethoxy)benzamide



Melting point: 209-210 ℃ (decomposition).
Washing solvent : diisopropyl ether.

Example 184

3-[1-(2,4-Dichlorobenzyl)-1H-indol-3-yl]-N-[4-[2-[[2-(dimethylamino)ethyl]amino]-2-oxoethyl]phenyl]propanamide

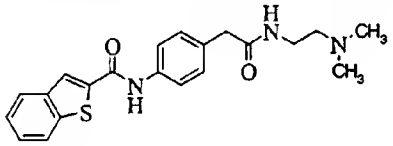


Melting point: : 123-125 ℃ (decomposition).

Washing solvent : diisopropyl ether.

Example 185

N-[4-[2-[[2-(Dimethylamino)ethyl]amino]-2-oxoethyl]phenyl]-1-benzothiophen-2-carboxamide

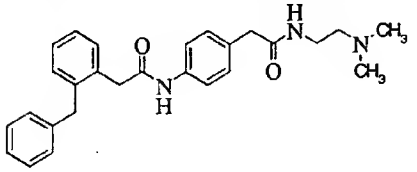


Melting point: 186-187 ℃ (decomposition).

Washing solvent : diisopropyl ether.

Example 186

2-(2-Benzylphenyl)-N-[4-[2-[[2-(dimethylamino)ethyl]amino]-2-oxoethyl]phenyl]acetamide

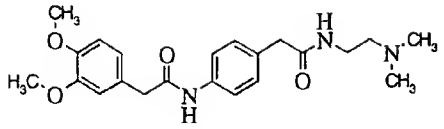


Melting point: 115-117 ℃.

Washing solvent : diisopropyl ether.

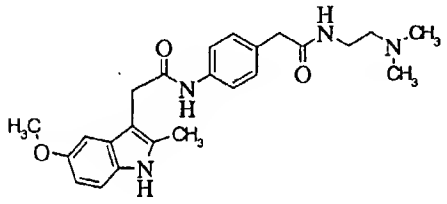
Example 187

2-(3,4-dimethoxyphenyl)-N-[4-[2-[[2-(dimethylamino)ethyl]amino]-2-oxoethyl]phenyl]acetamide



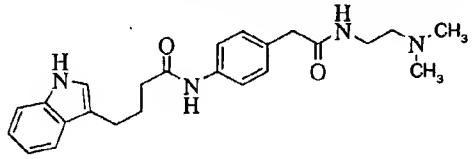
Melting point: 123-124 ℃.
Recrystallization solvent : methanol - diisopropyl ether.

Example 188
N-[4-[2-[[2-(Dimethylamino)ethyl]amino]-2-oxoethyl]phenyl]-2-(5-methoxy-2-methyl-1H-indol-3-yl)acetamide



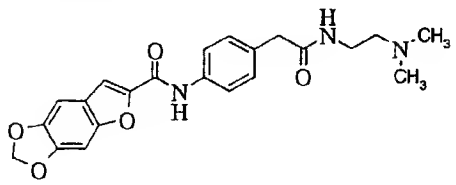
Melting point: 125-126 ℃.
Recrystallization solvent : methanol - diisopropyl ether.

Example 189
N-[4-[2-[[2-(Dimethylamino)ethyl]amino]-2-oxoethyl]phenyl]-4-(1H-indol-3-yl)butanamide



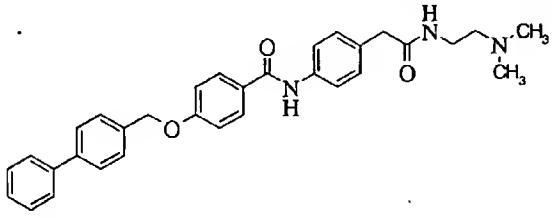
Melting point: 132-133 ℃.
Washing solvent : diisopropyl ether.

Example 190
N-[4-[2-[[2-(Dimethylamino)ethyl]amino]-2-oxoethyl]phenyl]furo[2,3-f][1,3]benzodioxol-6-carboxamide



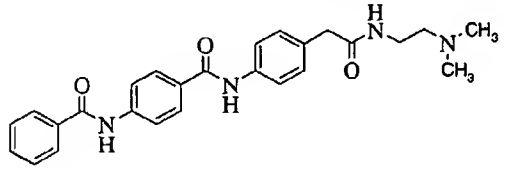
Melting point: : 173-175 ℃ (decomposition).
Washing solvent : diisopropyl ether.

Example 191
4-([1,1'-Biphenyl]-4-ylmethoxy)-N-[4-[2-[[2-(dimethylamino)ethyl]amino]-2-oxoethyl]phenyl]benzamide



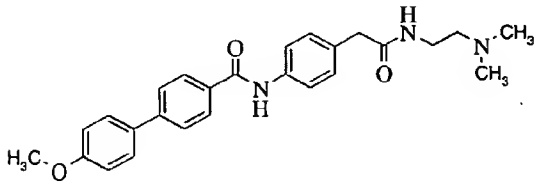
Melting point: 204-208 ℃.
Washing solvent : diisopropyl ether.

Example 192
4-(Benzoylamino)-N-[4-[2-[[2-(dimethylamino)ethyl]amino]-2-oxoethyl]phenyl]benzamide



Melting point: 220-221 ℃.
Washing solvent : diisopropyl ether.

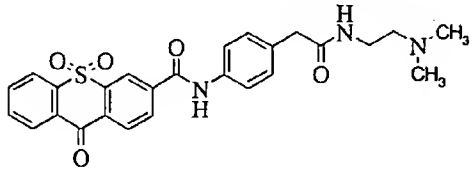
Example 193
N-[4-[2-[[2-(Dimethylamino)ethyl]amino]-2-oxoethyl]phenyl]-4'-methoxy[1,1'-biphenyl]-4-carboxamide



Melting point: 196-198 ℃ (decomposition).
Washing solvent : diisopropyl ether.

Example 194

N-[4-[2-[[2-(Dimethylamino)ethyl]amino]-2-oxoethyl]phenyl]-9,10,10-trioxo-9,10-dihydro-10λ⁶-thioxanten-3-carboxamide

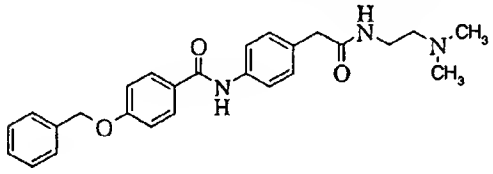


Melting point: : 162-163 ℃ (decomposition).

Washing solvent : diisopropyl ether.

Example 195

4-(Benzyloxy)-N-[4-[2-[[2-(dimethylamino)ethyl]amino]-2-oxoethyl]phenyl]benzamide

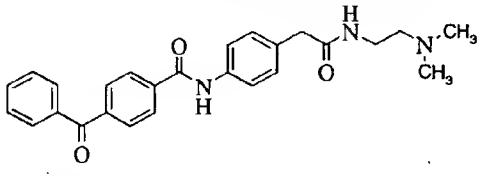


Melting point: 190-192 ℃ (decomposition).

Washing solvent : diisopropyl ether.

Example 196

4-Benzoyl-N-[4-[2-[[2-(dimethylamino)ethyl]amino]-2-oxoethyl]phenyl]benzamide

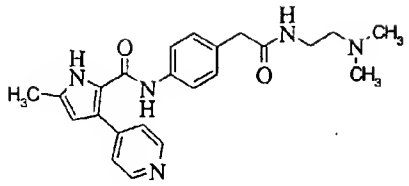


Melting point: 173-175 ℃ (decomposition).

Washing solvent : diisopropyl ether.

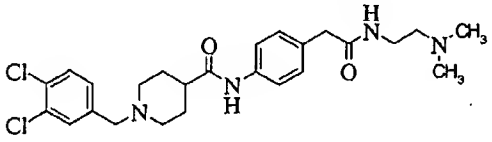
Example 197

N-[4-[2-[[2-(Dimethylamino)ethyl]amino]-2-oxoethyl]phenyl]-5-methyl-3-(4-pyridinyl)-1H-pyyrole-2-carboxamide



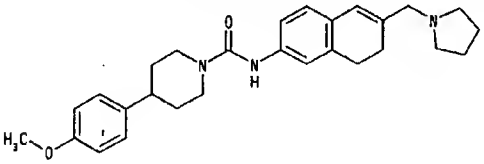
Melting point: : 215-218 ℃ (decomposition).
Washing solvent : diisopropyl ether.

Example 198
1-(3,4-Dichlorobenzyl)-N-[4-[2-[[2-(dimethylamino)ethyl]amino]-2-oxoethyl]phenyl]-4-piperidinecarboxamide



Melting point: : 182-183 ℃ (decomposition).
Washing solvent : diisopropyl ether.

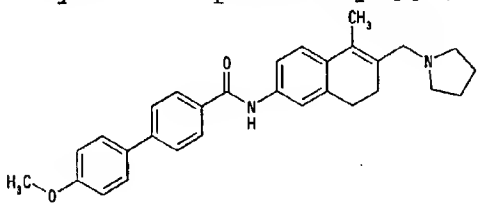
Example 199
4-(4-Methoxyphenyl)-N-[6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl]-1-piperidinecarboxamide



The titled compound was obtained by carrying out the same operation as in Example 99, using 6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 54.
^{1}H-NMR ($CDCl_3$) δ : 1.61-1.91 (8H, m), 2.31 (2H, t, J=8.1 Hz), 2.54 (4H, m), 2.73-2.81 (3H, m), 2.98 (2H, t, J=7.8 Hz), 3.16 (2H, s), 3.79 (3H, s), 4.20 (2H, d, J=13.1 Hz), 6.31 (1H, s), 6.36 (1H, s), 6.86 (2H, d, J=8.6 Hz), 7.06-7.20 (5H, m).
Melting point: 175-176 ℃ (crystallization solvent : ethyl acetate - diisopropyl ether)

Example 200

4'-Methoxy-N-[6-(1-pyrrolidinylmethyl)-5-methyl-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained by carrying out the same operation as in Example 1, using 5-methyl-6-(1-pyrrolidinylmethyl)- 7,8-dihydro-2-naphthalenamine obtained in Reference Example 69.

^{1}H-NMR ($CDCl_3$) δ: 1.78 (4H, m), 2.10 (3H, s), 2.37 (2H, t, J=8.1 Hz), 2.53 (4H, m), 2.76 (2H, t, J=8.1 Hz), 3.28 (2H, s), 3.87 (3H, s), 7.01 (2H, d, J=8.6 Hz), 7.27 (1H, d, J=7.8 Hz), 7.46 (1H, d, J=7.8 Hz), 7.48 (1H, s), 7.57 (2H, d, J=8.6 Hz), 7.66 (2H, d, J=8.4 Hz), 7.81 (1H, s), 7.92 (2H, d, J=8.4 Hz).

Elemental analysis for $C_{30}H_{32}N_2O_2$

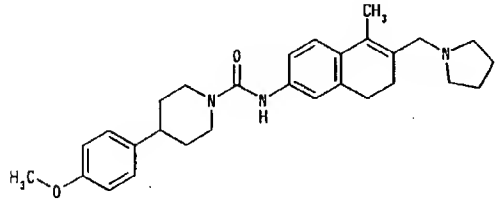
Calcd.: C, 79.61; H, 7.13; N, 6.19

Found: C, 79.35; H, 7.28; N, 6.24

Melting point: 179-180 ℃ (crystallization solvent: ethyl acetate - diisopropyl ether)

Example 201

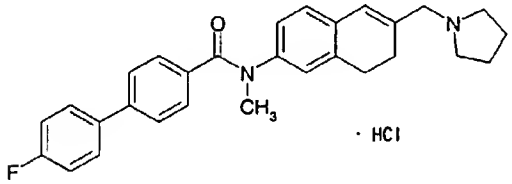
4-(4-Methoxyphenyl)-N-[6-(1-pyrrolidinylmethyl)-5-methyl-7,8-dihydro-2-naphthalenyl]-1-piperidinecarboxamide



The titled compound was obtained by carrying out the same operation as in Example 99, using 5-methyl-6-(1-pyrrolidinylmethyl)- 7,8-dihydro-2-naphthalenamine

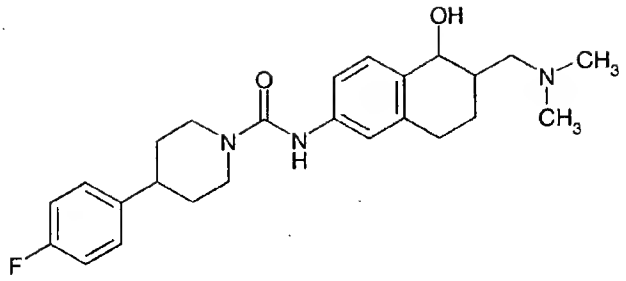
obtained in Reference Example 69.
^{1}H-NMR ($CDCl_3$) δ: 1.67 (2H, dd, J=13.4, 4.0 Hz), 1.78 (4H, m), 1.89 (2H, d, J=11.4 Hz), 2.07 (3H, s), 2.34 (2H, t, J=7.5 Hz), 2.52 (4H,m), 2.68-2.73 (3H, m), 2.98 (2H, t, J=7.5 Hz), 3.26 (2H, s), 3.80 (3H, s), 4.20 (2H, d, J=13.4 Hz), 6.36 (1H, s), 6.86 (2H, d, J=8.4 Hz), 7.12-7.20 (5H, m).
Elemental analysis for $C_{28}H_{37}N_3O_2$
Calcd.: C, 75.13; H, 8.33; N, 9.39
Found: C, 74.96; H, 8.14; N, 9.10
Melting point: 163-164 ℃ (crystallization solvent: ethyl acetate - diisopropyl ether)

Example 202
4'-Fluoro-N-methyl-N-[6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide hydrochloride



The titled compound was obtained by carrying out the same operation as in Example 1, using N-methyl6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine hydrochloride obtained in Reference Example 95.
^{1}H-NMR (DMSO-d_6) δ: 1.92-1.98 (4H, m), 2.39 (2H, t, J=8.1 Hz), 2.73 (2H, t, J=8.1 Hz), 3.00 (2H, m), 3.35 (3H, m), 3.44 (2H, m), 3.83 (2H, d, J=5.6 Hz), 6.62 (1H, s), 6.92-7.01 (2H, m), 7.11 (1H, s), 7.26 (2H, dd, J=8.9, 5.6 Hz), 7.38 (2H, d, J=8.1 Hz), 7.55 (2H, d, J=8.1 Hz), 7.69 (2H, dd, J=8.9, 5.6 Hz), 10.60 (1H, brs).
FABMS(pos) 441.2 $[M+H]^+$

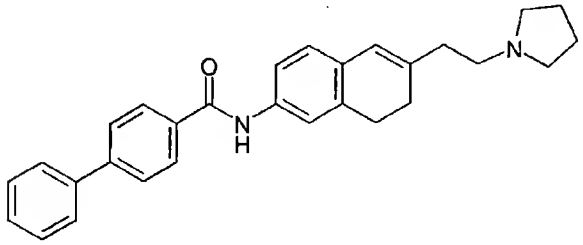
Example 203
N-[6-[(Dimethylamino)methyl]-5-hydroxy-5,6,7,8-tetrahydro-2-naphthalenyl]-4-(4-fluorophenyl)-1-piperidinecarboxamide



N, N—Dimethylmethylene ammonium chloride(638 mg, 6.82 mmol) was added to a mixed solution of 4-(4-fluorophenyl)-N-(5-oxo-5,6,7,8-tetrahydro-2-naphthalenyl)-1-piperidinecarboxamide (1.00 g, 2.73 mmol) obtained in Reference Example 97 in tetrahydrofuran (10 ml) and acetonitrile (10 ml), which was stirred at room temperature for 1 day. The solvent was distilled out under reduced pressure. Ethyl acetate was added to the residue, which was washed with aqueous potassium carbonate solution and saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then the solvent was distilled out under reduced pressure. The resulting oily substance was dissolved in methanol (15 ml). Sodium borohydride (103 mg, 2.73 mmol) was added to the solution under ice-cooling, which was stirred for 1 hour. Then, the solvent was distilled out under reduced pressure. 1N Hydrochloric acid was added to the residue, which was washed with ethyl acetate. 4N Sodium hydroxide was added to the water layer to make it alkaline. The reaction mixture was extracted with ethyl acetate, which was washed with saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then the solvent was distilled out under reduced pressure. The resulting residue was purified by aluminum B column chromatography (development solvent; ethyl acetate), powdered with hexane, to give the titled compound (231 mg).
Melting point: 160-163 ℃ (crystallization solvent: ethyl acetate - n-hexane)
FAB(pos) 426.3 [M+H]+

Example 204

N-[6-[2-(1-Pyrrolidinyl)ethyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide

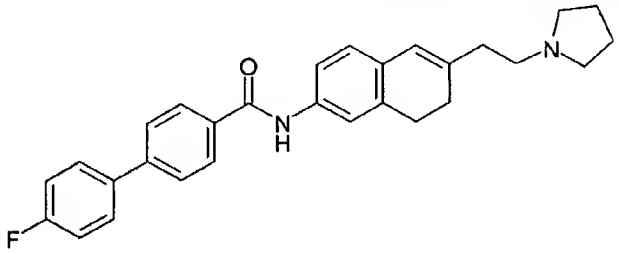


Concentrated hydrochloric acid (2 ml) was added to N-[6-[2-(1-pyrrolidinyl)ethyl]-7,8-dihydro-2-naphthalenyl]acetamide (98.0 mg, 0.345 mmol) obtained in Reference Example 103, which was stirred at 100 ℃ for 16 hours. The solvent was distilled out under reduced pressure. Ethyl acetate was added to the residue, which was washed with aqueous potassium carbonate solution and saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then the solvent was distilled out under reduced pressure. WSC (62.5 mg, 0.326 mmol) was added to a dimethylformamide solution (1.5ml) of the resulting oily substance (79.0 mg, 0.326 mmol), [1,1'-biphenyl]-4-carboxylic acid (64.6 mg, 0.326 mmol) and DMAP (39.8 mg, 0.326 mmol) under ice-cooling, which was stirred at room temperature for 1 day. Ethyl acetate was added to the reaction mixture, washed with aqueous potassium carbonate solution and saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, then the solvent was distilled out under reduced pressure. The resulting residue was purified by aluminum column chromatography (development solvent ; ethyl acetate), powdered with ethyl acetate and isopropyl ether (1:5) , to give the titled compound (36.8 mg).

^{1}H NMR (DMSO-d_6) δ : 1.67 (4H, m), 2.23 (2H, m), 2.34 (2H, m), 2.46 (4H, m), 2.57 (2H, m), 2.75 (2H, m), 6.24 (1H, s), 6.98 (1H, d, J = 8.1 Hz), 7.40-7.59 (5H, m), 7.76 (2H, d, J = 7.5 Hz), 7.82 (2H, d, J=8.4 Hz), 8.05 (2H, d, J = 8.4

Hz), 10.19 (1H, s).
Melting point: 184-186 ℃ (crystallization solvent : ethyl acetate - isopropyl ether)
FAB(pos) 423.2 [M+H]+

Example 205
4'-Fluoro-N-[6-[2-(1-pyrrolidinyl)ethyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



Concentrated hydrochloric acid (2 ml) was added to N-[6-[2-(1-pyrrolidinyl)ethyl]-7,8-dihydro-2-naphthalenyl]acetamide (98.0 mg, 0.345 mmol) obtained in Reference Example 103, which was stirred at 100℃ for 16 hours. The solvent was distilled out under reduced pressure. Ethyl acetate was added to the residue, which was washed with aqueous potassium carbonate solution and saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then the solvent was distilled out under reduced pressure. WSC (62.5 mg, 0.326 mmol) was added to a dimethylformamide solution (1.5 ml) of the resulting oily substance (79.0 mg, 0.326 mmol), 4'-fluoro-[1,1'-biphenyl]-4-carboxylic acid (64.6 mg, 0.326 mmol) and DMAP (39.8 mg, 0.326 mmol) under ice-cooling, which was stirred at room temperature for 1 day. Ethyl acetate was added to the reaction mixture, which was washed with aqueous potassium carbonate solution and saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and the solvent was distilled out under reduced pressure. The resulting residue was purified by aluminum column chromatography (development solvent ; ethyl acetate), powdered with ethyl acetate -

isopropyl ether (1:5), to give the titled compound (75.1 mg).

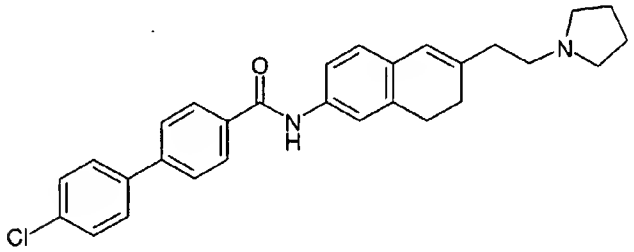
^{1}H NMR (DMSO-d_6) δ: 1.68 (4H, m), 2.23 (2H, m), 2.35 (2H, m), 2.50 (4H, m), 2.59 (2H, m), 2.75 (2H, m), 6.24 (1H, s), 6.98 (1H, d, J = 8.1 Hz), 7.34 (2H, m), 7.56 (2H, m), 7.81 (4H, m), 8.04 (2H, d, J = 8.4 Hz), 10.19 (1H, s).

Melting point: 187-189℃ (crystallization solvent: ethyl acetate - isopropyl ether)

FAB (pos) 441.3 [M+H]+

Example 206

4'-Chloro-N-[6-[2-(1-pyrrolidinyl)ethyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



Concentrated hydrochloric acid (2 ml) was added to N-[6-[2-(1-pyrrolidinyl)ethyl]-7,8-dihydro-2-naphthalenyl]acetamide (98.0 mg, 0.345 mmol) obtained in Reference Example 103, which was stirred at 100℃ for 16 hours. The solvent was distilled out under reduced pressure. Ethyl acetate was added to the residue, which was washed with aqueous potassium carbonate solution and saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then the solvent was distilled out under reduced pressure. WSC (62.5 mg, 0.326 mmol) was added to a dimethylformamide solution (1.5 ml) of the resulting oily substance (79.0 mg, 0.326 mmol), 4'-chloro-[1,1'-biphenyl]-4-carboxylic acid (64.6 mg, 0.326 mmol) and DMAP (39.8 mg, 0.326 mmol) under ice-cooling, which was stirred at room temperature for 1 day. Ethyl acetate was added to the reaction mixture, which was washed with aqueous potassium carbonate solution and

saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then the solvent was distilled out under reduced pressure. The resulting residue was purified by aluminum column chromatography (development solvent ; ethyl acetate), powdered with ethyl acetate - isopropyl ether (1:5), to give the titled compound (78.4 mg).

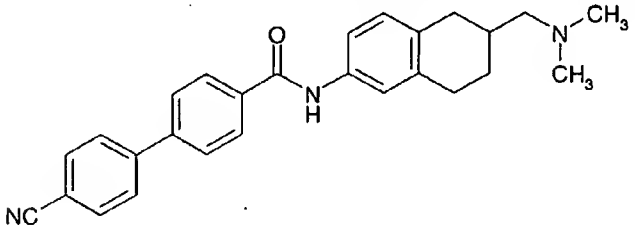
^{1}H NMR (DMSO-d_6) δ : 1.67 (4H, m), 2.23 (2H, m), 2.34 (2H, m), 2.45 (4H, m), 2.57 (2H, m), 2.75 (2H, m), 6.24 (1H, s), 6.98 (1H, d, J = 8.1 Hz), 7.55 (4H, m), 7.80 (2H, d, J=8.4 Hz), 7.84 (2H, d, J=8.4 Hz), 8.05 (2H, d, J = 8.7 Hz), 10.20 (1H, s).

Melting point: 207-209℃ (crystallization solvent: ethyl acetate - isopropyl ether)

FAB (pos) 457.2 [M+H]+

Example 207

4'-Cyano-N-[6-[(dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained by carrying out the same operation as in Example 1, using N-[(6-amino-1,2,3,4-tetrahydro-2-naphthalenyl)methyl]-N,N-dimethylamine and 4'-cyano-[1,1'-biphenyl]-4-carboxylic acid.

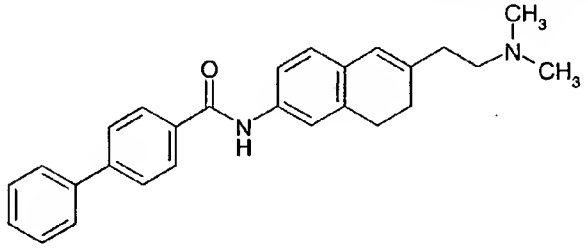
^{1}H NMR ($CDCl_3$) δ : 1.42 (1H, m), 1.95 (2H, m), 2.26 (6H, s), 2.24-2.46 (3H, m), 2.84-2.95 (3H, m), 7.10 (1H, d, J=8.4 Hz), 7.30 (1H, m), 7.46 (1H, s), 7.74 (7H, m), 7.98 (2H, d, J=8.4 Hz).

Melting point: 183-185℃ (crystallization solvent: ethyl acetate - isopropyl ether)

FAB (pos) 410.2 [M+H]+

Example 208

N-[6-[2-(Dimethylamino)ethyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide

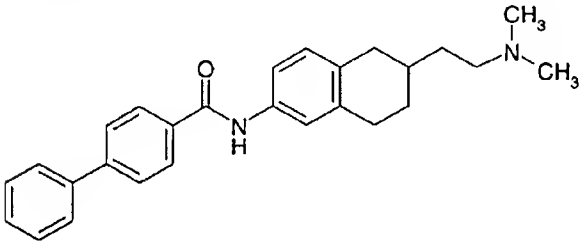


Concentrated hydrochloric acid (1.5 ml) was added to N-[6-[2-(dimethylamino)ethyl]-7,8-dihydro-2-naphthalenyl]acetamide (57.5 mg, 0.223 mmol) obtained in Reference Example 104, which was stirred at 100℃ for 1 hour. The solvent was distilled out under reduced pressure. Ethyl acetate was added to the residue, which was washed with aqueous potassium carbonate solution and saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then the solvent was distilled out under reduced pressure. WSC (29.2 mg, 0.139 mmol) was added to a dimethylformamide solution (0.7 ml) of the resulting oily substance (30 mg, 0.139 mmol), [1,1'-biphenyl]-4-carboxylic acid (30.2 mg, 0.139 mmol) and DMAP (16.9 mg, 0.139 mmol) under ice-cooling, which was stirred at room temperature for 16 hours. Ethyl acetate was added to the reaction mixture, which was washed with aqueous potassium carbonate solution and saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then the solvent was distilled out under reduced pressure. The resulting residue was purified by aluminum column chromatography (development solvent ; ethyl acetate), powdered with ethyl acetate - isopropyl ether (1:5), to give the titled compound (12.4 mg).

^{1}H NMR ($CDCl_3$) δ : 2.29 (8H, m), 2.41 (2H, m), 2.46 (2H, m), 2.84 (2H, t, J = 8.1 Hz), 6.24 (1H, s), 6.98 (1H, d, J = 8.4 Hz), 7.34 (1H, m), 7.41 (1H, d, J = 6.9 Hz), 7.46 (3H,

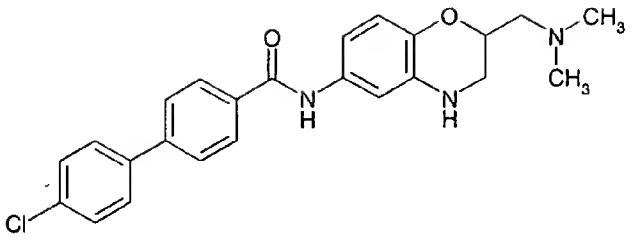
m), 7.63 (2H, d, J = 7.2 Hz), 7.71 (2H, d, J = 8.4 Hz), 7.77 (1H, br), 7.94 (2H, d, J = 8.4 Hz).
Melting point: 148-150℃ (crystallization solvent : ethyl acetate - isopropyl ether)
FAB (pos) 397.2 [M+H]+

Example 209
N-[6-[2-(Dimethylamino)ethyl]-5,6,7,8-tetrahydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



A methanol solution (5 ml) of N-[6-[2-(dimethylamino)ethyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide (20 mg, 0.050 mmol) obtained in Example 208 and palladium carbon (10 mg) was stirred under hydrogen atmosphere for 4 hours. After a catalyst was filtered off, the filtrate was concentrated under reduced pressure. The resulting residue was purified by aluminum B column chromatography (development solvent ; ethyl acetate), powdered with ethyl acetate - hexane (1:3) , to give the titled compound (4.0 mg).
^{1}H NMR ($CDCl_3$) δ : 1.60 (4H, m), 1.92 (1H, m), 2.26 (6H, s), 2.42 (3H, m), 2.84 (3H, m), 7.06 (1H, d, J=8.1Hz), 7.32 (1H, m), 7.46 (4H, m), 7.63 (2H, d, J=6.9Hz), 7.72 (3H, m), 7.94 (2H, d, J=8.1Hz).
Melting point: 112-114℃ (crystallization solvent : ethyl acetate - isopropyl ether)
FAB(pos) 399.2 [M+H]+

Example 210
4'-Chloro-N-[2-[(dimethylamino)methyl]-3,4-dihydro-2H-1,4-benzoxazin-6-yl][1,1'-biphenyl]-4-carboxamide



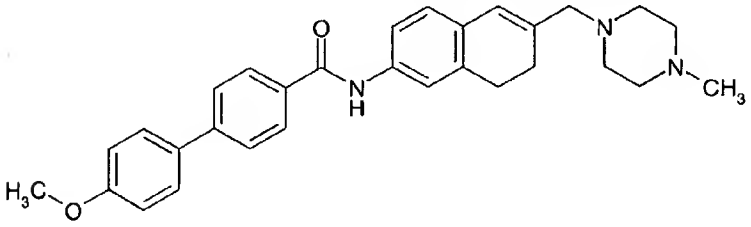
The titled compound was obtained as white powders by the same method as in Example 1, using 6-amino-2-(dimethylamino)methyl-1,4-benzoxazin obtained in Reference Example 105.

^{1}H-NMR ($CDCl_3$) δ : 2.33 (6H, s), 2.44-2.65 (2H, m), 3.15-3.21 (1H, m), 3.41-3.46 (1H, m), 3.87 (1H, brs), 4.24-4.26 (1H, m), 6.61 (1H, dd, J=2.5, 8.6 Hz), 6.81 (1H, d, J=8.6 Hz), 7.28 (1H, d, J=2.5 Hz), 7.43 (2H, d, J=6.5 Hz), 7.54 (2H, d, J=6.5 Hz), 7.64 (2H, d, J=8.4 Hz), 7.71 (1H, s), 7.90 (2H, d, J=8.4 Hz).

Melting point: 227-230 ℃ (crystallization solvent: diisopropyl ether)

Example 211

4'-Methoxy-N-[6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



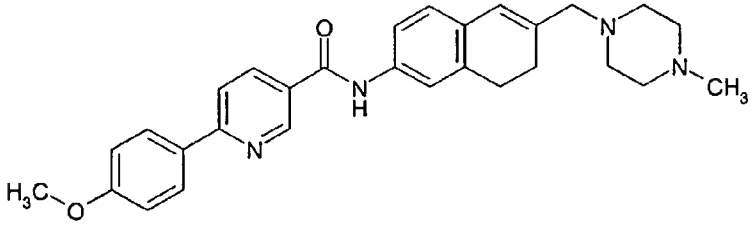
The titled compound was obtained as colorless powders by carrying out the same operation as in Example 1, using 6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenamine obtained in Reference Example 106.

^{1}H NMR ($CDCl_3$) δ : 2.31 (3H, s), 2.33 (2H, t, J=8.1 Hz), 2.49 (8H, bs), 2.84 (2H, t, J=8.1 Hz), 3.07 (2H, s), 3.87 (3H, s), 6.36 (1H, s), 7.00-7.03 (3H, m), 7.36 (1H, d, J=8.1 Hz), 7.51 (1H, s), 7.58 (2H, d, J=8.4 Hz), 7.67 (2H, d, J=8.4 Hz), 7.78 (1H, s), 7.91 (2H, d, J=8.4 Hz).

Melting point: 208-210 ℃ (crystallization solvent: ethyl acetate)

Example 212

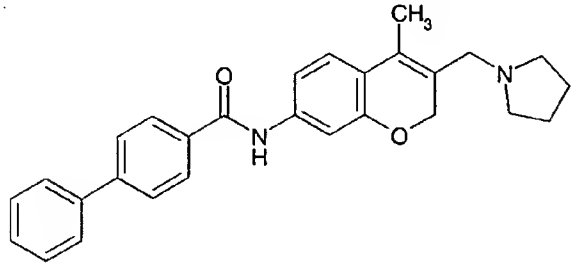
6-(4-Methoxyphenyl)-N-[6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenyl]nicotinamide



The titled compound was obtained as colorless powders by carrying out the same operation as in Example 1, using 6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenamine obtained in Reference Example 106.
^{1}H NMR ($CDCl_3$) δ: 2.30 (3H, s), 2.33 (2H, t, J=8.1 Hz), 2.47 (8H, bs), 2.84 (2H, t, J=8.1 Hz), 3.07 (2H, s), 3.89 (3H, s), 6.36 (1H, s), 7.01-7.04 (3H, m), 7.37 (1H, d, J=8.1 Hz), 7.49 (1H, s), 7.78-7.81 (2H, m), 8.03 (2H, d, J=8.4 Hz), 8.21 (1H, dd, J=2.1 Hz, 8.7 Hz), 9.09 (1H, s).
Melting point: 235-237 ℃ (crystallization solvent: ethyl acetate)

Example 213

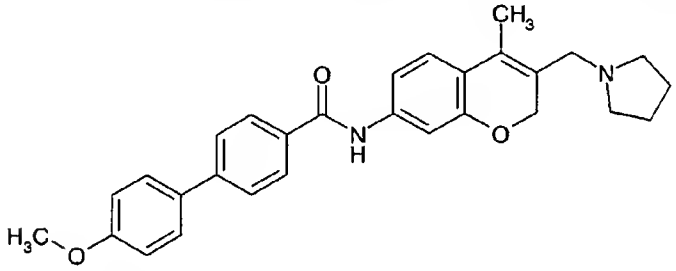
N-[4-Methyl-3-(1-pyrrolidinylmethyl)-2H-chromen-7-yl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained as colorless powders by carrying out the same operation as in Example 1, using

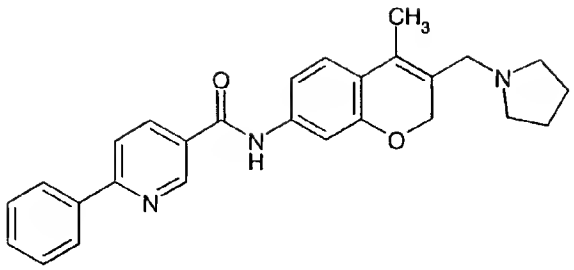
4-methyl-3-(1-pyrrolidinylmethyl)-2H-chromen-7-amine obtained in Reference Example 107.
^{1}H NMR ($CDCl_3$) δ: 1.77 (4H, s), 2.05 (3H, s), 2.51 (4H, s), 3.25 (2H, s), 4.74 (2H, s), 7.14-7.50 (6H, m), 7.63 (2H, d, J=7.2 Hz), 7.71 (2H, d, J=8.4 Hz), 7.79 (1H, s), 7.94 (2H, d, J=8.4 Hz).
Melting point: 176-178 ℃ (crystallization solvent: ethyl acetate - diisopropyl ether)

Example 214
4'-Methoxy-N-[4-methyl-3-(1-pyrrolidinylmethyl)-2H-chromen-7-yl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained as colorless powders by carrying out the same operation as in Example 1, using 4-methyl-3-(1-pyrrolidinylmethyl)-2H-chromen-7-amine obtained in Reference Example 107.
^{1}H NMR ($CDCl_3$) δ: 1.77 (4H, s), 2.05 (3H, s), 2.51 (4H, s), 3.25 (2H, s), 3.87 (3H, s), 4.74 (2H, s), 7.01 (2H, d, J=8.7 Hz), 7.14-7.31 (3H, m), 7.57 (2H, d, J=8.7 Hz), 7.66 (2H, d, J=8.4 Hz), 7.89 (1H, s), 7.91 (2H, d, J=8.4 Hz).
Melting point: 195-197 ℃ (crystallization solvent: ethyl acetate - diisopropyl ether)

Example 215
N-[4-Methyl-3-(1-pyrrolidinylmethyl)-2H-chromen-7-yl]-6-phenylnicotinamide



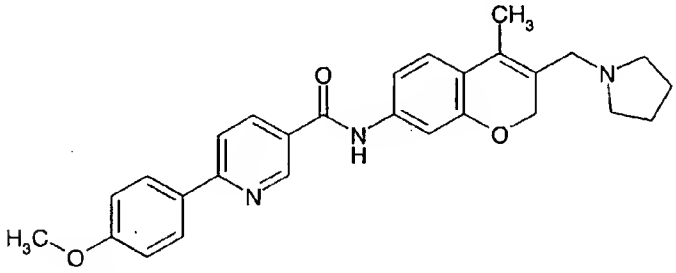
The titled compound was obtained as colorless powders by carrying out the same operation as in Example 1, using 4-methyl-3-(1-pyrrolidinylmethyl)-2H-chromen-7-amine obtained in Reference Example 107.

^{1}H NMR ($CDCl_3$) δ: 1.77 (4H, s), 2.05 (3H, s), 2.51 (4H, s), 3.25 (2H, s), 4.74 (2H, s), 7.14-7.28 (3H, m), 7.47-7.54 (3H, m), 7.81-7.87 (2H, m), 8.06 (2H, d, J=8.4 Hz), 8.27 (1H, d, J=8.4 Hz), 9.13 (1H, s).

Melting point: 192-193 ℃ (crystallization solvent: ethyl acetate)

Example 216

6-(4-Methoxyphenyl)-N-[4-methyl-3-(1-pyrrolidinylmethyl)-2H-chromen-7-yl]nicotinamide



The titled compound was obtained as colorless powders by carrying out the same operation as in Example 1, using 4-methyl-3-(1-pyrrolidinylmethyl)-2H-chromen-7-amine obtained in Reference Example 107.

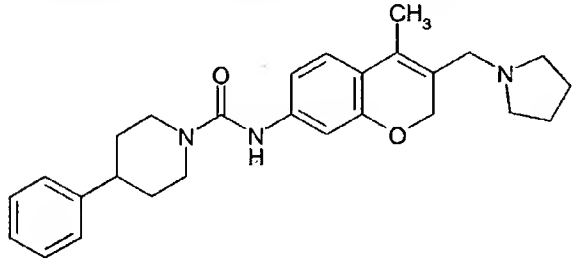
^{1}H NMR ($CDCl_3$) δ: 1.77 (4H, s), 2.05 (3H, s), 2.51 (4H, s), 3.25 (2H, s), 3.89 (3H, s), 4.74 (2H, s), 7.03 (2H, d, J=8.7 Hz), 7.14-7.26 (3H, m), 7.75-7.81 (2H, m), 8.03 (2H, d, J=8.7 Hz), 8.21 (1H, d, J=6.6 Hz), 9.09 (1H, s).

Melting point: 201-203 ℃ (crystallization solvent: ethyl

acetate)

Example 217

N-[4-Methyl-3-(1-pyrrolidinylmethyl)-2H-chromen-7-yl]-4-phenyl-1-piperidinecarboxamide



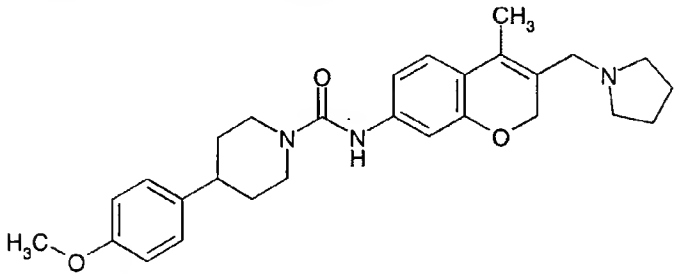
The titled compound was obtained as colorless powders by carrying out the same operation as in Example 99, using 4-methyl-3-(1-pyrrolidinylmethyl)-2H-chromen-7-amine obtained in Reference Example 107.

^{1}H NMR ($CDCl_3$) δ : 1.72-1.95 (8H, m), 2.03 (3H, s), 2.54 (4H, s),2.63-2.76 (1H, m), 2.95-3.00 (2H, m), 3.27 (2H, s), 4.19-4.23 (2H, m), 4.70 (2H, s), 6.39 (1H, s), 6.83 (1H, s), 7.01-7.32 (7H, m).

Melting point: 125-127 ℃ (crystallization solvent: ethyl acetate - diisopropyl ether)

Example 218

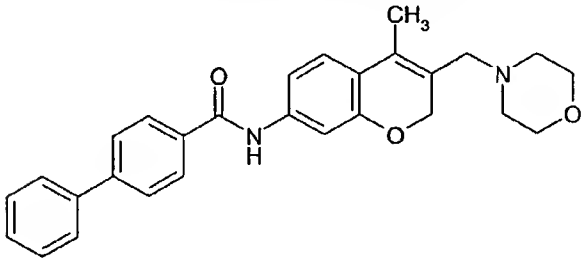
4-(4-Methoxyphenyl)-N-[4-methyl-3-(1-pyrrolidinylmethyl)-2H-chromen-7-yl]-1-piperidinecarboxamide



The titled compound was obtained as colorless powders by carrying out the same operation as in Example 99, using 4-methyl-3-(1-pyrrolidinylmethyl)-2H-chromen-7-amine

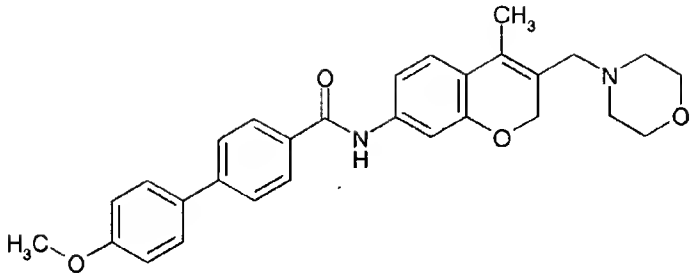
obtained in Reference Example 107.
^{1}H NMR ($CDCl_3$) δ: 1.63-1.91 (8H, m), 2.02 (3H, s), 2.49 (4H, s), 2.61-2.71 (1H, m), 2.93-3.01 (2H, m), 3.23 (2H, s), 3.79 (3H, s), 4.16-4.21 (2H, m), 4.69 (2H, s), 6.34 (1H, s), 6.82-6.91 (3H, m), 6.99-7.02 (1H, m), 7.10-7.15 (3H, m).
Melting point: 144-146 ℃ (crystallization solvent: ethyl acetate - n-hexane)

Example 219
N-[4-Methyl-3-(4-morpholinylmethyl)-2H-chromen-7-yl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained as colorless powders by carrying out the same operation as in Example 1, using 4-methyl-3-(4-morpholinylmethyl)-2H-chromen-7-amine obtained in Reference Example 108.
^{1}H NMR (DMSO-d_6) δ: 2.01 (3H, s), 2.37 (4H, s), 3.32 (2H, s), 3.57 (4H, s), 4.63 (2H, s), 7.23 (1H, d, J=8.1 Hz), 7.38-7.54 (5H, m), 7.76 (2H, d, J=7.5 Hz), 7.84 (2H, d, J=8.1 Hz), 8.04 (2H, d, J=8.1 Hz), 10.27 (1H, s).
Melting point: 162-164 ℃ (crystallization solvent: ethyl acetate - diisopropyl ether)

Example 220
4'-Methoxy-N-[4-methyl-3-(4-morpholinylmethyl)-2H-chromen-7-yl][1,1'-biphenyl]-4-carboxamide



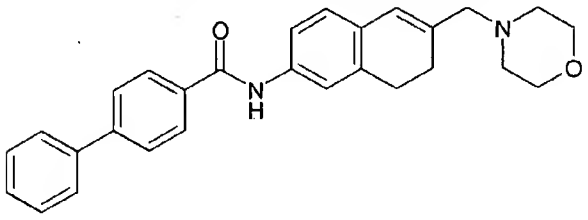
The titled compound was obtained as colorless powders by carrying out the same operation as in Example 1, using 4-methyl-3-(4-morpholinylmethyl)-2H-chromen-7-amine obtained in Reference Example 108.

^{1}H NMR (DMSO-d_6) δ: 2.00 (3H, s), 2.37 (4H, s), 3.11 (2H, s), 3.57 (4H, s), 3.82 (3H, s), 4.63 (2H, s),7.07 (2H, d, J=8.7 Hz), 7.23 (1H, d, J=8.1 Hz), 7.38-7.40 (2H, m), 7.72 (2H, d, J=8.7 Hz), 7.79 (2H, d, J=8.4 Hz), 8.01 (2H, d, J=8.4 Hz), 10.23 (1H, s).

Melting point: 198-200 ℃ (crystallization solvent: ethyl acetate - diisopropyl ether

Example 221

N-[6-(4-Morpholinylmethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained as colorless powders by carrying out the same operation as in Example 1, using 6-(4-morpholinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 109.

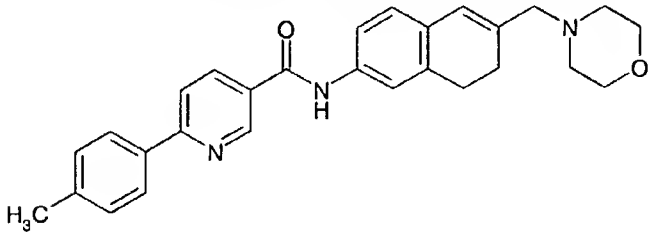
^{1}H-NMR ($CDCl_3$) δ: 2.34 (2H, t, J=8.4 Hz), 2.45 (4H, m), 2.85 (2H, t, J=8.4 Hz), 3.06 (2H, s), 3.73 (4H, t, J=4.7 Hz), 6.36 (1H, s), 7.02 (1H, d, J=8.1 Hz), 7.36-7.78 (10H, m), 7.93 (2H, d, J=8.1 Hz).

Melting point: 180-181 ℃ (crystallization solvent:

ethyl acetate - diisopropyl ether)

Example 222

6-(4-Methylphenyl)-N-[6-(4-morpholinylmethyl)-7,8-dihydro-2-naphthalenyl]nicotinamide



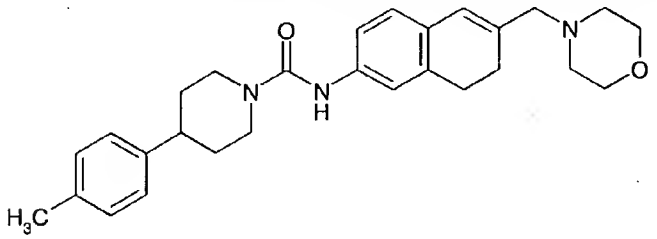
The titled compound was obtained as colorless powders by carrying out the same operation as in Example 1, using 6-(4-morpholinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 109.

^{1}H-NMR ($CDCl_3$) δ : 2.39 (2H, t, J=8.4 Hz), 2.43 (7H, m), 2.85 (2H, t, J=8.4 Hz), 3.06 (2H, s), 3.73 (4H, t, J=4.5 Hz), 6.36 (1H, s), 7.03 (1H, d, J=8.1 Hz), 7.30-7.38 (3H, m), 7.50 (1H, s), 7.76 (1H, s), 7.84 (1H, d, J=8.1 Hz), 7.97 (2H, d, J=8.1 Hz), 8.24 (1H, dd, J=8.4, 2.3 Hz), 9.12 (1H, s).

Melting point: 233-234 ℃ (crystallization solvent: ethyl acetate - diisopropyl ether)

Example 223

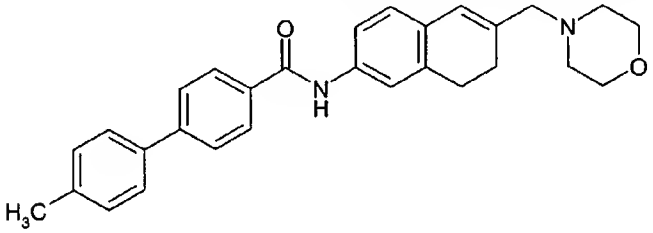
4-(4-Methylphenyl)-N-[6-(4-morpholinylmethyl)-7,8-dihydro-2-naphthalenyl]-1-piperidinecarboxamide



The titled compound was obtained as colorless powders by carrying out the same operation as in Example 99, using 6-(4-morpholinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 109.

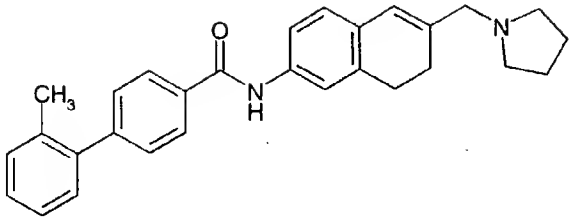
^{1}H-NMR ($CDCl_3$) δ : 1.65-1.75 (4H, m), 1.90 (2H, m), 2.27-2.43 (7H, m), 2.72 (1H, m), 2.79 (2H, t, J=7.5 Hz), 2.93-3.04 (4H, m), 3.72 (4H, m), 4.20 (2H, d, J=11.7 Hz), 6.31 (1H, s), 6.39 (1H, s), 6.92 (1H, d, J=8.1 Hz), 7.05-7.26 (6H, m).
Melting point: 231-214 ℃ (crystallization solvent: ethyl acetate - diisopropyl ether)

Example 224
4'-Methyl-N-[6-(4-morpholinylmethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



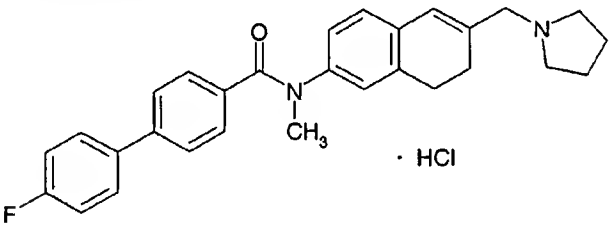
The titled compound was obtained as colorless powders by carrying out the same operation as in Example 1, using 6-(4-morpholinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 109.
^{1}H-NMR ($CDCl_3$) δ : 2.33 (2H, t, J=8.1 Hz), 2.42-2.44 (7H, m), 2.84 (2H, t, J=8.1 Hz), 3.06 (2H, s), 3.72 (4H, t, J=4.2 Hz), 6.36 (1H, s), 7.01 (1H, d, J=8.1 Hz), 7.25-7.29 (2H, m), 7.37 (1H, d, J=8.1 Hz), 7.51-7.54 (3H, m), 7.68 (2H, d, J=8.1 Hz), 7.85 (1H, s), 7.92 (2H, d, J=8.1 Hz).
Melting point: 196-197 ℃ (crystallization solvent: ethyl acetate - diisopropyl ether)

Example 225
2'-Methyl-N-[6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained as colorless powders by carrying out the same operation as in Example 1, using 6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 54.
Melting point: 177-178 ℃ (crystallization solvent: ethyl acetate - diisopropyl ether)

Example 226
4'-Fluoro-N-methyl-N-[6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide Hydrochloride



N-Methyl-6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine dihydrochloride (315 mg, 1.0 mmol) obtained in Reference Example 113 was dissolved in N,N-dimethylformamide (25 ml). 4-Bromobenzoic acid (402 mg, 2.0 mmol), WSC (383 mg, 2.0 mmol), HOBt (270 mg, 2.0 mmol) and DMAP (244mg, 2.0 mmol) were added to the solution, which was stirred at room temperature for 16 hours. Ethyl acetate and water were added to the reaction mixture, and extraction was conducted. The ethyl acetate layer was concentrated under reduced pressure. The residue was purified by aluminum column chromatography (development solvent ; ethyl acetate : n-hexane = 33:67). The eluate was concentrated under reduced pressure, which was dissolved in dimethoxyethane - tetrahydrofuran (10:1, 5.5 ml).

4-Fluorophenylboric acid (73 mg, 0.52 mmol), tetrakis(triphenylphosphine)palladium complex (15 mg, 0.013 mmol) and 2N aqueous sodium carbonate solution (0.433 ml) were added to the solution, which was refluxed with heating under nitrogen atmosphere at 90℃ for 5.5 hours. The reaction mixture was poured into cold water, and extraction was conducted using ethyl acetate. The ethyl acetate layer was concentrated, and the residue was purified by aluminum column chromatography (development solvent; ethyl acetate). 4N Hydrogen chloride - ethyl acetate solution was added to the eluate, which was concentrated under reduced pressure. The resulting residue was recrystallized from methanol - ethyl acetate, to give the titled compound (108 mg).

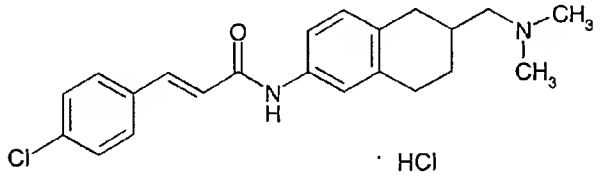
^{1}H-NMR (DMSO-d_6) δ: 1.92-1.98 (4H, m), 2.39 (2H, t, J=8.1 Hz), 2.73 (2H, t, J=8.1 Hz), 3.00 (2H, m), 3.35 (3H, m), 3.44 (2H, m), 3.83 (2H, d, J=5.6 Hz), 6.62 (1H, s), 6.92-7.01 (2H, m), 7.11 (1H, s), 7.26 (2H, dd, J=8.9, 5.6 Hz), 7.38 (2H, d, J=8.1 Hz), 7.55 (2H, d, J=8.1 Hz), 7.69 (2H, dd, J=8.9, 5.6 Hz), 10.60 (1H, brs.).

Melting point: 201-203 ℃ (crystallization solvent: methanol - diisopropyl ether)

FAB(pos) 441.2 [M+H]+

Example 227

(E)-3-(4-Chlorophenyl)-N-[6-[(dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]-2-propenamide Hydrochloride

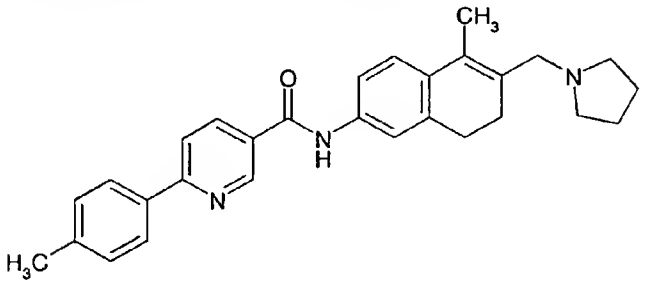


The titled compound was obtained as colorless powders by carrying out the same operation as in Example 4.

Melting point: 243-245 ℃ (crystallization solvent: methanol - diisopropyl ether)

Example 228

6-(4-Methylphenyl)-N-[5-methyl-6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl]nicotinamide



The titled compound was obtained as colorless powders by carrying out the same operation as in Example 1, using 5-methyl-6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 69.

Melting point: 175-176 ℃ (crystallization solvent: ethyl acetate - diisopropyl ether)

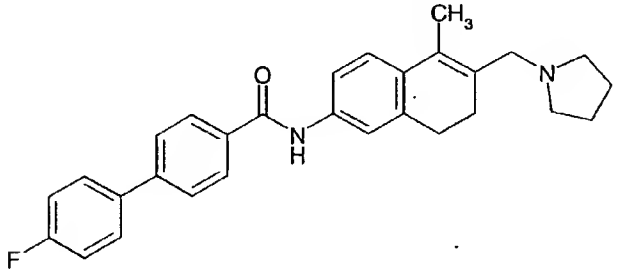
Elemental analysis for $C_{29}H_{30}N_3O$

Calcd.: C, 79.78; H, 6.93; N, 9.63

Found: C, 79.66; H, 6.97; N, 9.68

Example 229

4'-Fluoro-N-[5-methyl-6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide

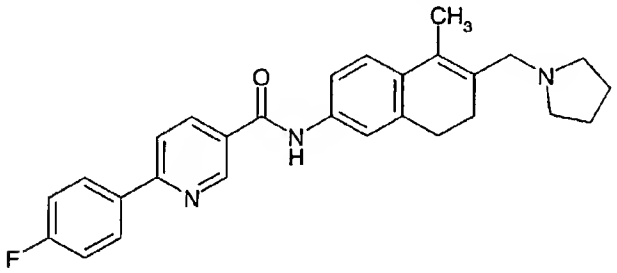


The titled compound was obtained as colorless powders by carrying out the same operation as in Example 1, using 5-methyl-6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 69.

Melting point: 199-201 ℃ (crystallization solvent: ethyl

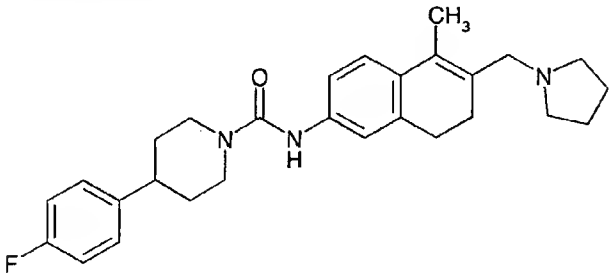
acetate - diisopropyl ether)
Elemental analysis for $C_{29}H_{30}FN_2O$
Calcd.: C, 79.06; H, 6.63; N, 6.36
Found: C, 79.01; H, 6.81; N, 6.45

Example 230
6-(4-Fluorophenyl)-N-[5-methyl-6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl]nicotinamide



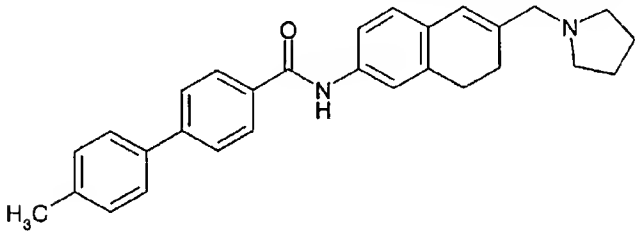
The titled compound was obtained as colorless powders by carrying out the same operation as in Example 1, using 5-methyl-6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 69.
Melting point: 204-205 ℃ (crystallization solvent: ethyl acetate - diisopropyl ether)
Elemental analysis for $C_{28}H_{28}FN_3O$
Calcd.: C, 76.17; H, 6.39; N, 9.52
Found: C, 76.03; H, 6.44; N, 9.62

Example 231
4-(4-Fluorophenyl)-N-[5-methyl-6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl]-1-piperidinecarboxamide



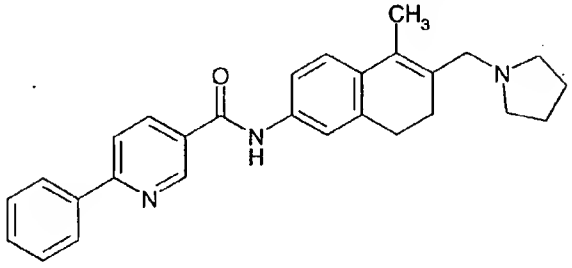
The titled compound was obtained as colorless powders by carrying out the same operation as in Example 99, using 5-methyl-6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 69.
Melting point: 172-173 ℃ (crystallization solvent: ethyl acetate - diisopropyl ether)

Example 232
4'-Methyl-N-[6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained as colorless powders by carrying out the same operation as in Example 1, using 6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 54.
Melting point: 176-177 ℃ (crystallization solvent: ethyl acetate - diisopropyl ether)

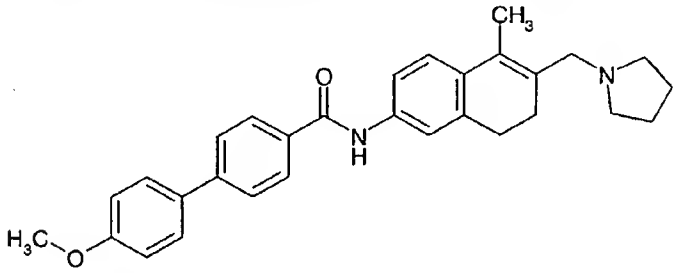
Example 233
N-[5-Methyl-6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl]-6-phenylnicotinamide



The titled compound was obtained as colorless powders by carrying out the same operation as in Example 1, using 5-methyl-6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 69.

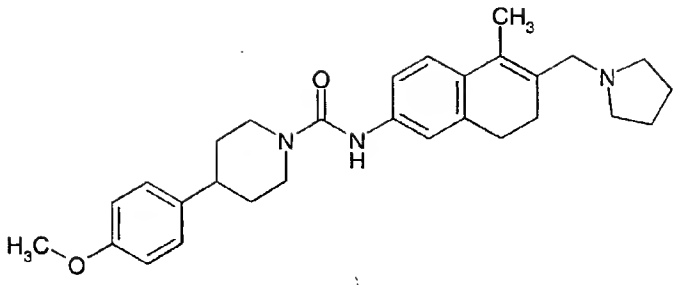
Melting point: 178-179 ℃ (crystallization solvent: ethyl acetate - diisopropyl ether)
Elemental analysis for $C_{28}H_{29}N_3O$
Calcd.: C, 79.40; H, 6.90; N, 9.92
Found: C, 79.13; H, 6.82; N, 10.03

Example 234
4'-Methoxy-N-[5-methyl-6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained as colorless powders by carrying out the same operation as in Example 1, using 5-methyl-6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 69.
^{1}H-NMR ($CDCl_3$) δ: 1.78 (4H,m), 2.10(3H,s), 2.37 (2H, t, J=8.1 Hz), 2.53 (4H, m), 2.76 (2H, t, J=8.1 Hz), 3.28(2H,s), 3.87 (3H, s), 7.01 (1H, d, J=8.6 Hz), 7.27 (2H, d, J=7.8 Hz), 7.46 (1H, d, J=7.8 Hz), 7.48 (1H, s), 7.57 (2H, d, J=8.6 Hz), 7.66 (2H, d, J=8.6 Hz), 7.81 (1H, s), 7.92 (2H, d, J=7.8 Hz).
Melting point: 179-180 ℃ (crystallization solvent: ethyl acetate - diisopropyl ether)
Elemental analysis for $C_{30}H_{32}N_2O_2$
Calcd.: C, 79.61; H, 7.13; N, 6.19
Found: C, 79.35; H, 7.28; N, 6.24

Example 235
4-(4-Methoxyphenyl)-N-[5-methyl-6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl]-1-piperidinecarboxamide



The titled compound was obtained as colorless powders by carrying out the same operation as in Example 99, using 5-methyl-6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 69.

^{1}H-NMR ($CDCl_3$) δ: 1.67 (2H, dd, J=13.4, 4.0 Hz), 1.78 (4H, m), 1.89 (2H, d, J=11.4 Hz), 2.07 (3H, s), 2.34 (2H, t, J=7.5 Hz), 2.52 (4H, m), 2.68-2.73 (3H, m), 2.98 (2H, t, J=7.5 Hz), 3.26 (2H, s), 3.80 (3H, s), 4.20 (2H, d, J=13.4 Hz), 6.36 (1H, s), 6.86 (2H, d, J=8.4 Hz), 7.12-7.20 (5H, m).

Melting point: 163-164 ℃ (crystallization solvent: ethyl acetate - diisopropyl ether)

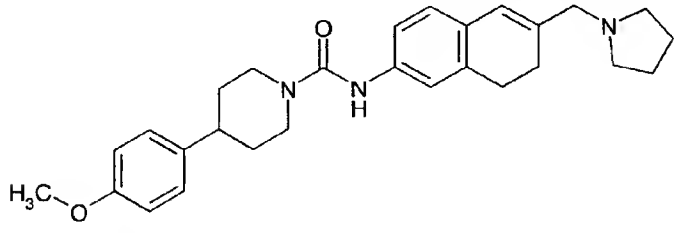
Elemental analysis for $C_{28}H_{37}N_3O_2$

Calcd.: C, 75.13; H, 8.33; N, 9.39

Found: C, 74.96; H, 8.14; N, 9.10

Example 236

4-(4-Methoxyphenyl)-N-[6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl]-1-piperidinecarboxamide



The titled compound was obtained as colorless powders by carrying out the same operation as in Example 1, using 6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 54.

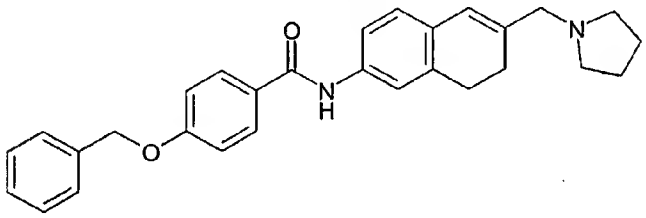
^{1}H-NMR ($CDCl_3$) δ: 1.61-1.91 (8H, m), 2.31 (2H, t, J=8.1 Hz), 2.54 (4H, m), 2.73-2.81 (3H, m), 2.98 (2H, t, J=7.8 Hz),

3.16 (2H, s), 3.79 (3H, s), 4.20 (2H, d, J=13.1 Hz), 6.31 (1H, s), 6.36 (1H, s), 6.86 (2H, d, J=8.6 Hz), 7.06-7.20 (5H, m).

Melting point: 175-176 ℃ (crystallization solvent: ethyl acetate - diisopropyl ether)

Example 237

4-(Benzyloxy)-N-[6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl]benzamide



The titled compound was obtained as colorless powders by carrying out the same operation as in Example 1, using 6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 54.

Melting point: 174-175 ℃ (crystallization solvent: ethyl acetate - diisopropyl ether)

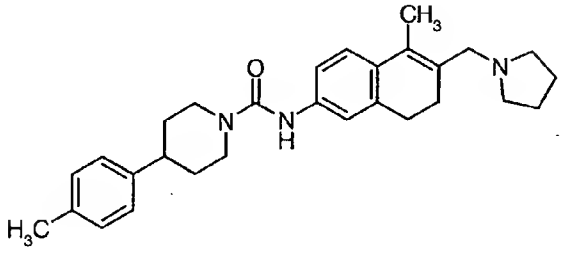
Elemental analysis for $C_{28}H_{30}N_2O_2$

Calcd.: C, 78.84; H, 7.09; N, 6.87

Found: C, 79.06; H, 6.99; N, 6.41

Example 238

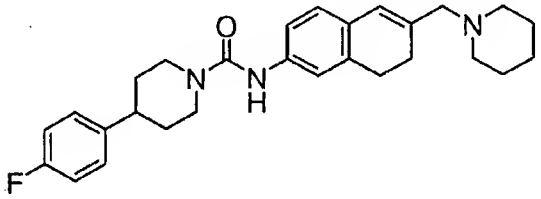
4-(4-Methylphenyl)-N-[5-methyl-6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl]-1-piperidinecarboxamide



The titled compound was obtained by carrying out the same operation as in Example 99, using 5-methyl-6-(1-

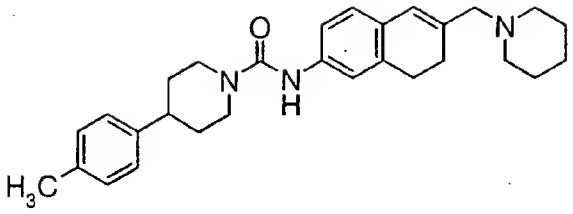
pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 69.
^{1}H-NMR ($CDCl_3$) δ: 1.65-1.78 (6H, m), 1.90 (2H, d, J=12.9 Hz), 2.07 (3H, s), 2.33-2.37 (5H, m), 2.53 (4H, m), 2.68-2.74 (3H, m), 2.99 (2H, m), 3.27(2H,s), 4.21 (2H, d, J=13.2 Hz), 6.37 (1H, s), 7.09-7.21 (7H, m).
Melting point: 159-160 ℃ (crystallization solvent: ethyl acetate - diisopropyl ether)
FAB(pos) 444.3 [M+H]+

Example 239
4-(4-Fluorophenyl)-N-[6-(1-piperidinylmethyl)-7,8-dihydro-2-naphthalenyl]-1-piperidinecarboxamide



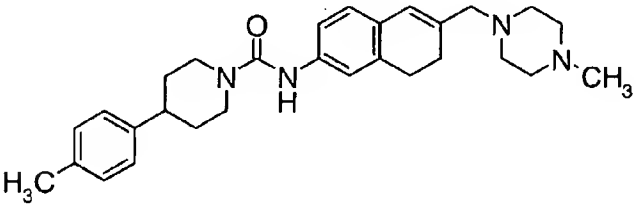
The titled compound was obtained by carrying out the same operation as in Example 99, using 6-(1-piperidinylmethyl)-7,8-dihydro-2-naphthalenamine dihydrochloride obtained in Reference Example 114.
^{1}H-NMR ($CDCl_3$) δ: 1.43 (2H, m), 1.56-1.75 (6H, m), 1.89 (2H, d, J=12.3 Hz), 2.27-2.36 (6H, m), 2.70 (1H, m), 2.78 (2H, t, J=7.5 Hz), 2.88-3.00 (4H, m), 4.20 (2H, d, J=13.2 Hz), 6.29 (1H, s), 6.38 (1H, s), 6.91-7.08 (4H, m), 7.14-7.20(3H, m).
Melting point: 194 -195 ℃ (crystallization solvent: ethyl acetate - diisopropyl ether)

Example 240
4-(4-Methylphenyl)-N-[6-(1-piperidinylmethyl)-7,8-dihydro-2-naphthalenyl]-1-piperidinecarboxamide



The titled compound was obtained by carrying out the same operation as in Example 99, using 6-(1-piperidinylmethyl)-7,8-dihydro-2-naphthalenamine dihydrochloride obtained in Reference Example 114.
^{1}H-NMR ($CDCl_3$) δ : 1.43 (2H, m), 1.56-1.74 (6H, m), 1.90 (2H, d, J=12.0 Hz), 2.27-2.36 (9H, m), 2.69 (1H, m), 2.79 (2H, t, J=8.1 Hz), 2.94-3.01 (4H, m), 4.19 (2H, d, J=13.2 Hz), 6.29 (1H, s), 6.35 (1H, s), 6.93(2H, d, J=8.1 Hz), 7.05-7.26 (5H, m).
Melting point: 209 -210 ℃ (crystallization solvent: ethyl acetate - diisopropyl ether)

Example 241
4-(4-Methylphenyl)-N-[6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenyl]-1-piperidinecarboxamide



The titled compound was obtained by carrying out the same operation as in Example 99, using 6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenamine obtained in Reference Example 106.
^{1}H NMR ($CDCl_3$) δ : 1.62-1.77 (2H, m), 1.90 (2H, d, J=12.0 Hz), 2.28 (2H, t, J=8.1 Hz), 2.29 (3H, s), 2.33 (3H, s), 2.46 (8H, bs), 2.64-2.73 (1H, m), 2.79 (2H, t, J=8.1 Hz), 2.96 (2H, d, J=10.5 Hz), 3.05 (2H, s), 4.19 (2H, d, J=13.5 Hz), 6.31 (1H, s), 6.34 (1H, s), 6.93 (1H, d, J=8.4 Hz), 7.04-7.16 (5H, m), 7.23 (1H, s).

Melting point: 214-216 ℃ (crystallization solvent: tetrahydrofuran - n-hexane)

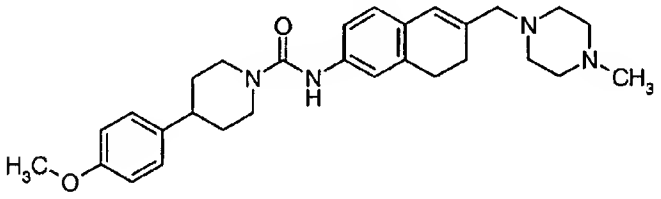
Elemental analysis for $C_{29}H_{38}N_4O$

Calcd.: C, 75.94; H, 8.35; N, 12.22.

Found: C, 75.67; H, 8.47; N, 12.27.

Example 242

4-(4-Methoxyphenyl)-N-[6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenyl]-1-piperidinecarboxamide



The titled compound was obtained by carrying out the same operation as in Example 99, using 6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenamine obtained in Reference Example 106.

^{1}H NMR ($CDCl_3$) δ: 1.68-1.76 (2H, m), 1.89 (2H, d, J=11.1 Hz), 2.29 (2H, t, J=8.1 Hz), 2.29 (3H, s), 2.46 (8H, bs), 2.64-2.71 (1H, m), 2.79 (2H, t, J=8.1 Hz), 2.82-3.03 (2H, m), 3.05 (2H, s), 3.80 (3H, s), 4.19 (2H, d, J=12.6 Hz), 6.31 (1H, s), 6.34 (1H, s), 6.87 (2H, d, J=8.7 Hz), 6.93 (1H, d, J=8.4 Hz), 7.06 (1H, dd, J=8.1, 2.1 Hz), 7.14 (2H, d, J=8.7 Hz), 7.23 (1H, s).

Melting point: 198-200 ℃ (crystallization solvent: tetrahydrofuran - n-hexane)

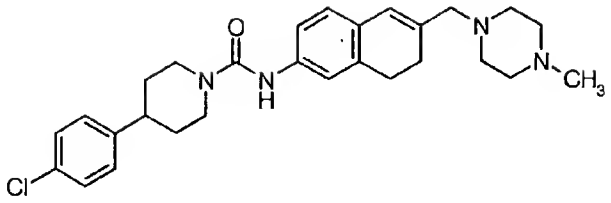
Elemental analysis for $C_{29}H_{38}N_4O_2$

Calcd.: C, 73.38; H, 8.07; N, 11.80.

Found : C, 73.04; H, 7.95; N, 11.67.

Example 243

4-(4-Chlorophenyl)-N-[6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenyl]-1-piperidinecarboxamide



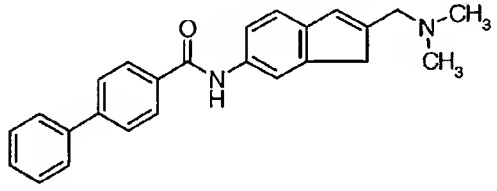
The titled compound was obtained by carrying out the same operation as in Example 99, using 6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenamine obtained in Reference Example 106.

^{1}H NMR ($CDCl_3$) δ: 1.64-1.76 (2H, m), 1.90 (2H, d, J=11.1 Hz), 2.29 (2H, t, J=8.1 Hz), 2.29 (3H, s), 2.46 (8H, bs), 2.66-2.72 (1H, m), 2.79 (2H, t, J=8.1 Hz), 2.81-3.03 (2H, m), 3.05 (2H, s), 4.20 (2H, d, J=12.6 Hz), 6.31 (1H, s), 6.34 (1H, s), 6.93 (1H, d, J=7.8 Hz), 7.04-7.07 (1H, m), 7.14 (2H, d, J=8.4 Hz), 7.22 (1H, s), 7.28 (2H, d, J=8.4 Hz).

Melting point: 201-203 ℃ (crystallization solvent: tetrahydrofuran - n-hexane)

Example 244

N-[2-[(Dimethylamino)methyl]-1H-inden-6-yl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained by carrying out the same operation as in Example 1, using 2-[(dimethylamino)methyl]-1H-inden-6-amine obtained in Reference Example 116.

Elemental analysis for $C_{25}H_{24}N_2O \cdot 0.5H_2O$

Calcd.: C, 79.55; H, 6.68; N, 7.42.

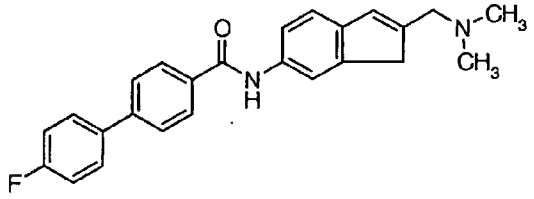
Found: C, 79.38; H, 6.76; N, 7.34.

Melting point: 187-189 ℃ (crystallization solvent: ethyl acetate - diisopropyl ether)

FAB(pos) 369.2 [M+H]+

Example 245

N-[2-[(Dimethylamino)methyl]-1H-inden-6-yl]-4'-fluoro[1,1'-biphenyl]-4-carboxamide



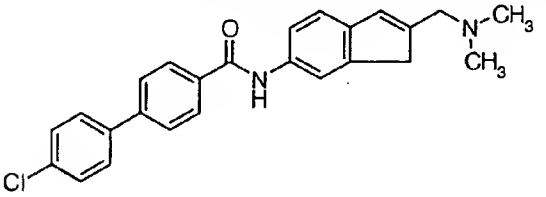
The titled compound was obtained by carrying out the same operation as in Example 1, using 2-[(dimethylamino)methyl]-1H-inden-6-amine obtained in Reference Example 116.

Melting point: 209-211 ℃ (crystallization solvent: ethyl acetate - diisopropyl ether)

FAB(pos) 387.2 [M+H]+

Example 246

4'-Chloro-N-[2-[(dimethylamino)methyl]-1H-inden-6-yl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained by carrying out the same operation as in Example 1, using 2-[(dimethylamino)methyl]-1H-inden-6-amine obtained in Reference Example 116.

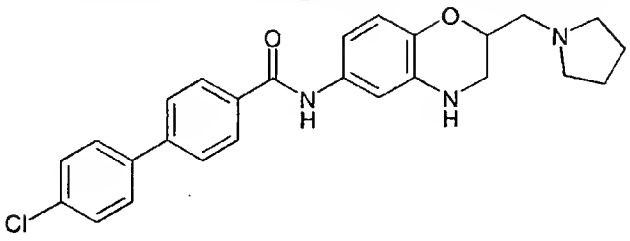
Melting point: 218-220 ℃ (crystallization solvent: ethyl acetate - diisopropyl ether)

FAB(pos) 403.2 [M+H]+

Example 247

4'-Chloro-N-[2-(1-pyrrolidinylmethyl)-3,4-dihydro-2H-

1,4-benzoxazin-6-yl][1,1'-biphenyl]-4-carboxamide



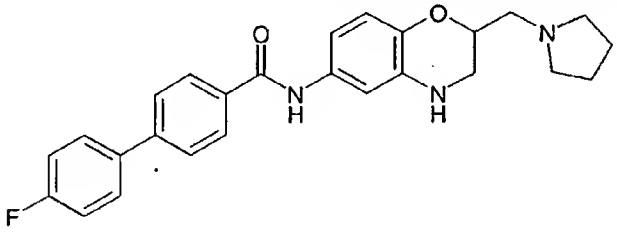
The titled compound was obtained by carrying out the same operation as in Example 1, using 6-amino-2-(1-pyrrolidinylmethyl)-3,4-dihydro-2H-1,4-benzoxazine obtained in Reference Example 117.

^{1}H-NMR ($CDCl_3$) δ: 1.70-1.90 (4H, m), 2.50-2.70 (4H, m), 2.73 (2H, d, J=6.0Hz), 3.18-3.24 (1H, m), 3.45-3.49 (1H, m), 3.87 (1H, brs), 4.26-4.28 (1H, m), 6.61 (1H, dd, J=2.7, 8.4 Hz), 6.80 (1H, d, J=8.4 Hz), 7.26 (1H, d, J=2.7 Hz), 7.44 (2H, d, J=8.4 Hz), 7.55 (2H, d, J=8.4 Hz), 7.64 (2H, d, J=8.1 Hz), 7.71 (1H, s), 7.91 (2H, d, J=8.1 Hz).

Melting point : 221-222 ℃ (crystallization solvent : diisopropyl ether)

Example 248

4'-Fluoro-N-[2-(1-pyrrolidinylmethyl)-3,4-dihydro-2H-1,4-benzoxazin-6-yl][1,1'-biphenyl]-4-carboxamide

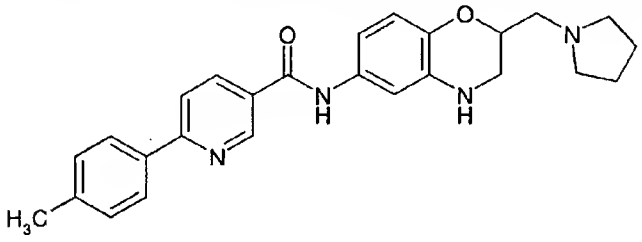


The titled compound was obtained by carrying out the same operation as in Reference Example 1, using 6-amino-2-(1-pyrrolidinylmethyl)-3,4-dihydro-2H-1,4-benzoxazine obtained in Reference Example 117.

^{1}H-NMR ($CDCl_3$) δ : 1.70-1.90 (4H, m), 2.50-2.70 (4H, m), 2.73 (2H, d, J =6.3Hz), 3.18-3.24 (1H, m), 3.45-3.49 (1H, m), 3.88(1H, brs), 4.24-4.30 (1H, m), 6.62 (1H, dd, J=2.7, 8.4 Hz), 6.80 (1H, d, J=8.4 Hz), 7.13-7.19 (2H, m), 7.26 (1H,

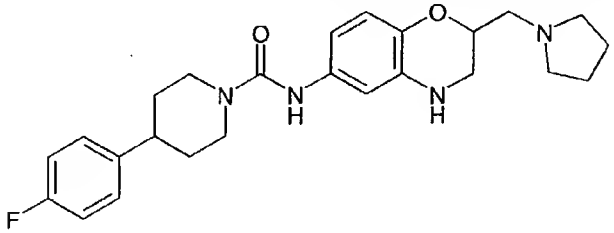
d, J=2.7 Hz), 7.56-7.60 (2H, m), 7.63 (2H, d, J=8.4 Hz), 7.71 (1H, s), 7.90 (2H, d, J=8.4 Hz).
Melting point : 204-206 ℃ (crystallization solvent : diisopropyl ether)

Example 249
6-(4-Methylphenyl)-N-[2-(1-pyrrolidinylmethyl)-3,4-dihydro-2H-1,4-benzoxazin-6-yl]nicotinamide



The titled compound was obtained by carrying out the same operation as in Reference Example 1, using 6-amino-2-(1-pyrrolidinylmethyl)-3,4-dihydro-2H-1,4-benzoxazine obtained in Reference Example 117.
^{1}H-NMR ($CDCl_3$) δ : 1.70-1.85 (4H, m), 2.43 (3H, s), 2.50-2.70 (4H, m), 2.74 (2H, d, J=6.3Hz), 3.19-3.25 (1H, m), 3.45-3.49 (1H, m), 3.90 (1H, brs), 4.27-4.29 (1H, m), 6.63 (1H, dd, J=2.4, 8.7 Hz), 6.81 (1H, d, J=8.7 Hz), 7.26 (1H, d, J=2.7 Hz), 7.31 (2H, d, J=8.1 Hz), 7.67 (1H, s), 7.81 (1H, d, J=8.1 Hz), 7.93 (2H, d, J=7.8Hz), 8.21 (1H, dd, J=2.4, 8.4 Hz), 9.09 (1H, d, J=2.4 Hz).
Melting point : 207-208 ℃ (crystallization solvent : diisopropyl ether)

Example 250
4-(4-Fluorophenyl)-N-[2-(1-pyrrolidinylmethyl)-3,4-dihydro-2H-1,4-benzoxazin-6-yl]-1-piperidinecarboxamide



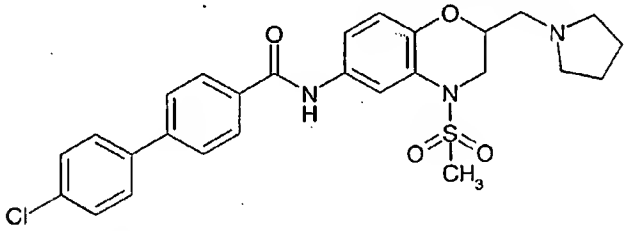
The titled compound was obtained by carrying out the same operation as in Reference Example 1, using 6-amino-2-(1-pyrrolidinylmethyl)-3,4-dihydro-2H-1,4-benzoxazine obtained in Reference Example 117.

^{1}H-NMR ($CDCl_3$) δ : 1.60-1.90 (8H, m), 2.50-2.70 (5H, m), 2.71 (2H, d, J=6.3Hz), 2.91-3.00 (2H, m), 3.15-3.21 (1H, brs), 3.42-3.45 (1H, m), 3.77 (1H, brs), 4.15-4.25 (3H, m), 6.20 (1H, s), 6.38 (1H, dd, J=2.1, 8.4 Hz), 6.73 (1H, d, J=8.4 Hz), 6.91 (1H, d, J=2.1 Hz), 6.97-7.03 (2H, m), 7.14-7.19 (2H, m).

Melting point : 192-195 ℃ (crystallization solvent : diisopropyl ether)

Example 251

4'-Chloro-N-[4-(methylsulfonyl)-2-(1-pyrrolidinylmethyl)-3,4-dihydro-2H-1,4-benzoxazin-6-yl][1,1'-biphenyl]-4-carboxamide



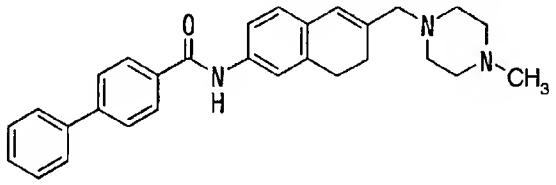
The titled compound was obtained by carrying out the same operation as in Reference Example 1, using 6-amino-4-(methylsulfonyl)-2-(1-pyrrolidinylmethyl)-3,4-dihydro-2H-1,4-benzoxazine obtained in Reference Example 118.

^{1}H-NMR ($CDCl_3$) δ : 1.75-1.85 (4H, m), 2.55-2.70 (4H, m), 2.78 (2H, d, J=6.0Hz), 3.04 (3H, s), 3.27-3.34 (1H, m), 4.24-4.31 (1H, m), 4.31-4.35 (1H, m), 6.98 (1H, d, J=8.7 Hz), 7.45 (2H, d, J=9.0 Hz), 7.50-7.60 (1H, m), 7.53 (2H, d, J=9.0 Hz), 7.67 (2H, d, J=8.4 Hz), 7.84 (1H, s), 7.84 (1H, brs), 7.94 (2H, d, J=8.4 Hz).

Melting point : 203-204 ℃ (crystallization solvent : diisopropyl ether)

Example 252

N-[6-[(4-Methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



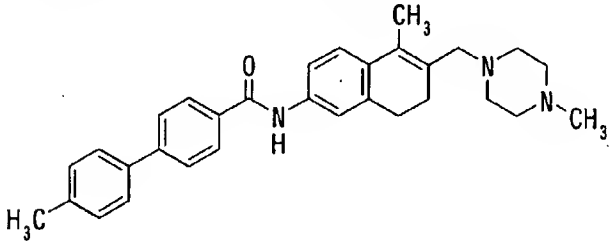
The titled compound was obtained by carrying out the same operation as in Reference Example 1, using 6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenamine obtained in Reference Example 106.

^{1}H NMR ($CDCl_3$) δ: 2.31 (3H, s), 2.33 (2H, t, J=8.1 Hz), 2.49 (8H, bs), 2.84 (2H, t, J=8.1 Hz), 3.07 (2H, s), 6.36 (1H, s), 7.02 (1H, d, J=8.1 Hz), 7.35-7.52 (5H, m), 7.63 (2H, d, J=8.1 Hz), 7.71 (2H, d, J=8.1 Hz), 7.80 (1H, s), 7.94 (2H, d, J=8.1 Hz).

Melting point: 196-198 ℃ (crystallization solvent: ethyl acetate)

Example 253

4'-Methyl-N-[5-methyl-6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide

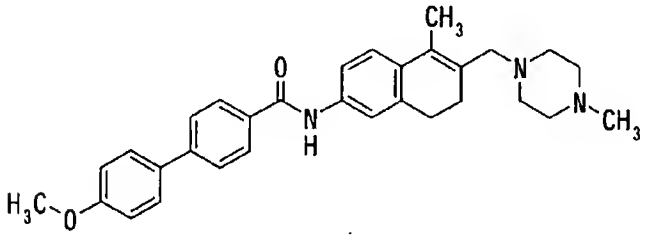


The titled compound was obtained by carrying out the same operation as in Reference Example 1, using 5-methyl-6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenamine obtained in Reference Example 115.

^{1}H NMR ($CDCl_3$) δ: 2.08 (3H, s), 2.29 (3H, s), 2.34 (2H, t, J=7.8 Hz), 2.42 (3H, s), 2.45 (8H, bs), 2.75 (2H, t, J=7.8 Hz), 3.16 (2H, s), 7.26-7.30 (3H, m), 7.44 (1H, d, J=8.4

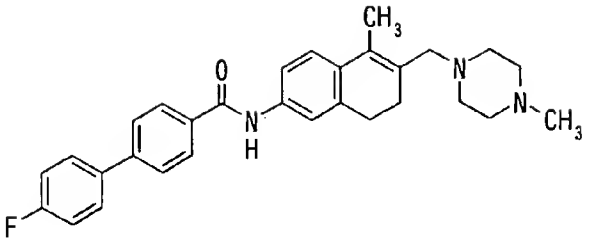
Hz), 7.53-7.55 (3H, m), 7.70 (2H, d, J=8.4 Hz), 8.00 (1H, s), 7.93 (2H, d, J=8.4 Hz).
Melting point: 212-214 ℃ (crystallization solvent: ethyl acetate)

Example 254
4'-Methoxy-N-[5-methyl-6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained by carrying out the same operation as in Reference Example 1, using 5-methyl-6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenamine obtained in Reference Example 115.
^{1}H NMR ($CDCl_3$) δ: 2.08 (3H, s), 2.29 (3H, s), 2.34 (2H, t, J=7.8 Hz), 2.45 (8H, bs), 2.75 (2H, t, J=7.8 Hz), 3.16 (2H, s), 3.87 (3H, s), 7.01 (2H, d, J=8.1 Hz), 7.27 (1H, d, J=8.4 Hz), 7.44 (1H, d, J=8.4 Hz), 7.51 (1H, s), 7.58 (2H, d, J=8.4 Hz), 7.67 (2H, d, J=8.4 Hz), 7.81 (1H, s), 7.92 (2H, d, J=8.4 Hz).
Melting point: 215-217 ℃ (crystallization solvent: ethyl acetate)

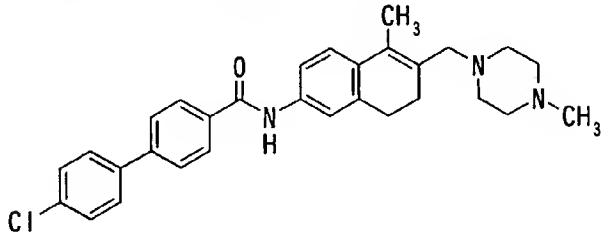
Example 255
4'-Fluoro-N-[5-methyl-6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained by carrying out the same operation as in Reference Example 1, using 5-methyl-6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenamine obtained in Reference Example 115.
^{1}H NMR ($CDCl_3$) δ: 2.08 (3H, s), 2.29 (3H, s), 2.34 (2H, t, J=7.8 Hz), 2.46 (8H, bs), 2.75 (2H, t, J=7.8 Hz), 3.16 (2H, s), 7.17 (2H, d, J=8.4 Hz), 7.28 (1H, d, J=8.4 Hz), 7.44 (1H, d, J=8.4 Hz), 7.51 (1H, s), 7.57-7.62 (2H, m), 7.66 (2H, d, J=8.4 Hz), 7.82 (1H, s), 7.94 (2H, d, J=8.4 Hz).
Melting point: 233-235 ℃ (crystallization solvent: ethyl acetate)

Example 256

4'-Chloro-N-[5-methyl-6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide

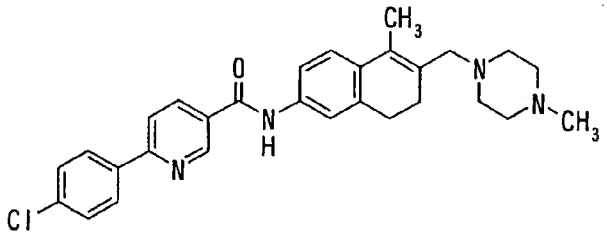


The titled compound was obtained by carrying out the same operation as in Reference Example 1, using 5-methyl-6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenamine obtained in Reference Example 115.
^{1}H NMR ($CDCl_3$) δ: 2.08 (3H, s), 2.29 (3H, s), 2.34 (2H, t, J=7.8 Hz), 2.46 (8H, bs), 2.75 (2H, t, J=7.8 Hz), 3.16 (2H, s), 7.28 (1H, d, J=8.4 Hz), 7.43-7.47 (3H, m), 7.51 (1H, s), 7.56 (2H, d, J=8.4 Hz), 7.67 (2H, d, J=8.4 Hz), 7.80 (1H, s), 7.94 (2H, d, J=8.4 Hz).

Melting point: 216-218 ℃ (crystallization solvent: ethyl acetate)

Example 257

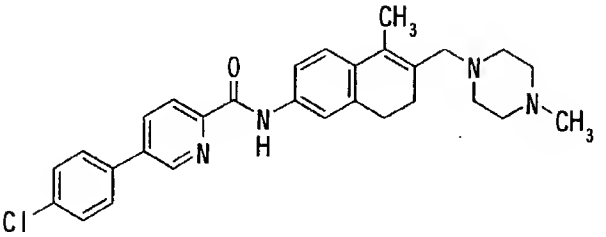
6-(4-Chlorophenyl)-N-[5-methyl-6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenyl]nicotinamide



The titled compound was obtained by carrying out the same operation as in Reference Example 1, using 5-methyl-6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenamine obtained in Reference Example 115.
^{1}H NMR ($CDCl_3$) δ: 2.09 (3H, s), 2.29 (3H, s), 2.35 (2H, t, J=8.1 Hz), 2.46 (8H, bs), 2.75 (2H, t, J=8.1 Hz), 3.16 (2H, s), 7.28 (1H, d, J=8.4 Hz), 7.43-7.50 (4H, m), 7.83 (2H, d, J=8.4 Hz), 8.01 (2H, d, J=8.4 Hz), 8.27 (1H, d, J=8.4 Hz), 9.13 (1H, s).
Melting point: 219-221 ℃ (crystallization solvent: ethyl acetate)

Example 258

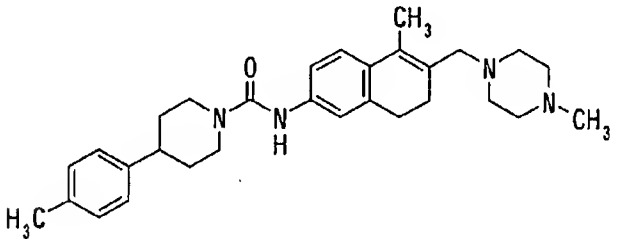
5-(4-Chlorophenyl)-N-[5-methyl-6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenyl]-2-pyridinecarboxamide



The titled compound was obtained by carrying out the same operation as in Reference Example 1, using 5-

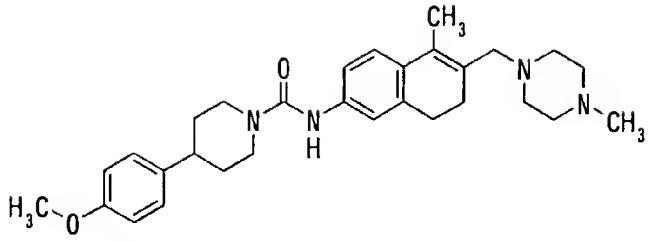
methyl-6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenamine obtained in Reference Example 115.
^{1}H NMR ($CDCl_3$) δ: 2.09 (3H, s), 2.29 (3H, s), 2.35 (2H, t, J=8.1 Hz), 2.45 (8H, bs), 2.77 (2H, t, J=8.1 Hz), 3.16 (2H, s), 7.30 (1H, d, J=8.1 Hz), 7.49-7.63 (6H, m), 8.05 (1H, dd, J=2.4 Hz, 8.4 Hz), 8.36 (1H, d, J=8.1 Hz), 8.79 (1H, d, J=1.2 Hz), 9.97 (1H, s).
Melting point: 177-179 ℃ (crystallization solvent: ethyl acetate)

Example 259
N-[5-Methyl-6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenyl]-4-(4-methylphenyl)-1-piperidinecarboxamide



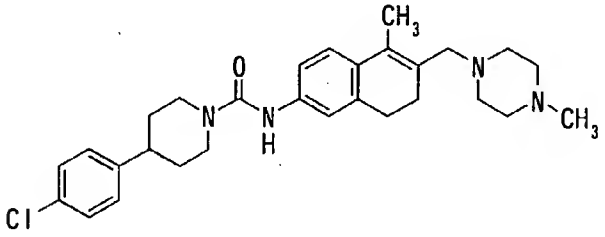
The titled compound was obtained by carrying out the same operation as in Reference Example 99, using 5-methyl-6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenamine obtained in Reference Example 115.
^{1}H NMR ($CDCl_3$) δ: 1.60-1.78 (4H, m), 2.05 (3H, s), 2.28 (3H, s), 2.29 (2H, t, J=8.1 Hz), 2.33 (3H, s), 2.46 (8H, bs), 2.65-2.72 (3H, m), 2.93-3.03 (2H, m), 3.13 (2H, s), 4.18-4.23 (2H, m), 6.40 (1H, s), 7.09-7.24 (7H, m).
Melting point: 176-178 ℃ (crystallization solvent: ethyl acetaten-hexane)

Example 260
4-(4-Methoxyphenyl)-N-[5-methyl-6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenyl]-1-piperidinecarboxamide



The titled compound was obtained by carrying out the same operation as in Reference Example 99, using 5-methyl-6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenamine obtained in Reference Example 115.
^{1}H NMR ($CDCl_3$) δ : 1.68-1.92 (4H, m), 2.05 (3H, s), 2.28 (3H, s), 2.29 (2H, t, J=8.1 Hz), 2.45 (8H, bs), 2.67-2.72 (3H, m), 2.95-3.02 (2H, m), 3.14 (2H, s), 3.80 (3H, s), 4.18-4.22 (2H, m), 6.36 (1H, s), 6.87 (2H, d, J=8.4 Hz), 7.12-7.21 (5H, m).
Melting point : 175-177 ℃ (crystallization solvent : ethyl acetate)

Example 261
4-(4-Chlorophenyl)-N-[5-methyl-6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenyl]-1-piperidinecarboxamide

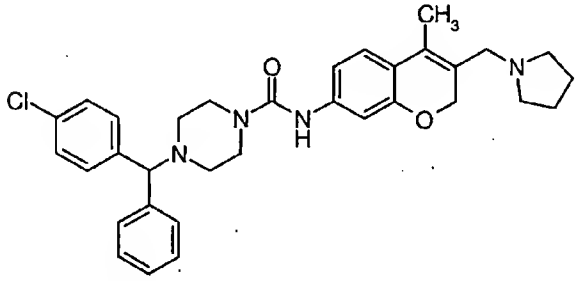


The titled compound was obtained by carrying out the same operation as in Reference Example 99, using 5-methyl-6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenamine obtained in Reference Example 115.
^{1}H NMR ($CDCl_3$) δ : 1.67-1.92 (4H, m), 2.05 (3H, s), 2.28 (3H, s), 2.29 (2H, t, J=8.1 Hz), 2.45 (8H, bs), 2.67-2.72 (3H, m), 2.95-3.02 (2H, m), 3.14 (2H, s), 4.18-4.23 (2H, m), 6.36 (1H, s), 7.13-7.30 (7H, m).
Melting point : 141-143 ℃ (crystallization solvent :

ethyl acetate)

Example 262

4-[(4-Chlorophenyl)(phenyl)methyl]-N-[4-methyl-3-(1-pyrrolidinylmethyl)-2H-chromen-7-yl]-1-piperazinecarboxamide



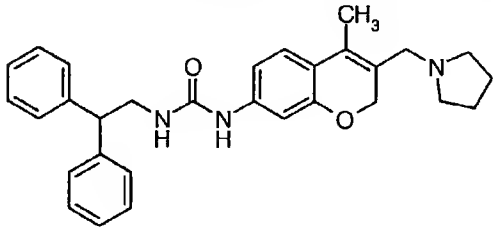
The titled compound was obtained by carrying out the same operation as in Reference Example 99, using 4-methyl-3-(1-pyrrolidinylmethyl)-2H-chromen-7-amine obtained in Reference Example 107.

^{1}H NMR ($CDCl_3$) δ: 1.76 (4H, s), 2.01 (3H, s), 2.42 (4H, t, J=5.1 Hz), 2.49 (4H, s), 3.22 (2H, s), 3.48 (4H, t, J=5.1 Hz), 4.24 (1H, s), 4.68 (2H, s), 6.23 (1H, s), 6.77 (1H, s), 6.96 (1H, d, J=8.7 Hz), 7.09 (1H, d, J=8.7 Hz), 7.19-7.61 (9H, m).

Melting point: 104-106 ℃ (crystallization solvent: ethyl acetate - n-hexane)

Example 263

N-(2,2-Diphenylethyl)-N'-[4-methyl-3-(1-pyrrolidinylmethyl)-2H-chromen-7-yl]urea



The titled compound was obtained by carrying out the same operation as in Reference Example 99, using 4-methyl-3-(1-pyrrolidinylmethyl)-2H-chromen-7-amine

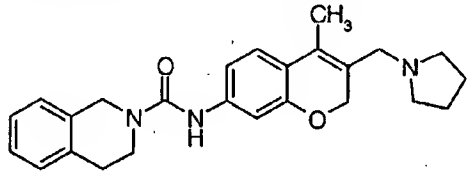
obtained in Reference Example 107.

^{1}H NMR ($CDCl_3$) δ: 1.76 (4H, s), 1.99 (3H, s), 2.49 (4H, s), 3.22 (2H, s), 3.83 (2H, t, J=7.8 Hz), 4.18 (1H, t, J=7.8 Hz), 4.66 (2H, s), 4.96 (1H, s), 6.48 (1H, s), 6.57 (1H, s), 6.69 (1H, d, J=8.1 Hz), 6.98 (1H, d, J=8.1 Hz), 7.20-7.30 (10H, m).

Melting point: 166-168 ℃ (crystallization solvent: ethyl acetate - n-hexane)

Example 264

N-[4-Methyl-3-(1-pyrrolidinylmethyl)-2H-chromen-7-yl]-3,4-dihydro-2(1H)-isoquinolinecarboxamide



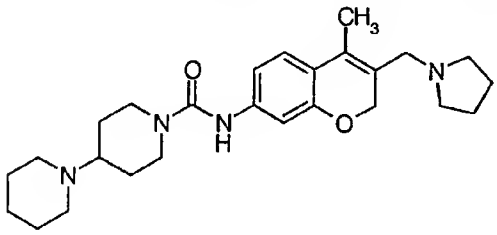
The titled compound was obtained by carrying out the same operation as in Reference Example 99, using 4-methyl-3-(1-pyrrolidinylmethyl)-2H-chromen-7-amine obtained in Reference Example 107.

^{1}H NMR ($CDCl_3$) δ: 1.76 (4H, s), 2.02 (3H, s), 2.49 (4H, s), 2.92 (2H, t, J=6.0 Hz), 3.23 (2H, s), 3.71 (2H, t, J=6.0Hz), 4.65 (2H, s), 4.68 (2H, s), 6.43 (1H, s), 6.86 (1H, d, J=1.8 Hz), 7.02-7.22 (6H, m).

Melting point: 135-137 ℃ (crystallization solvent: ethyl acetate - n-hexane)

Example 265

N-[4-Methyl-3-(1-pyrrolidinylmethyl)-2H-chromen-7-yl]-4-(1-piperidinyl)-1-piperidinecarboxamide



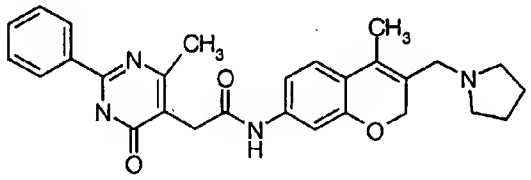
The titled compound was obtained by carrying out the same operation as in Reference Example 99, using 4-methyl-3-(1-pyrrolidinylmethyl)-2H-chromen-7-amine obtained in Reference Example 107.

^{1}H NMR ($CDCl_3$) δ: 1.27-1.89 (14H, m), 2.02 (3H, s), 2.49-2.51 (9H, m), 2.83-2.90 (2H, m), 3.23 (2H, s), 4.08-4.12 (2H, m), 4.68 (2H, s), 6.31 (1H, s), 6.80 (1H, d, J=2.4 Hz), 6.98 (1H, dd, J=2.4 Hz, 8.4 Hz), 7.09 (1H, d, J=8.4 Hz).

Melting point: 98-100 ℃ (crystallization solvent: ethyl acetate - n-hexane)

Example 266

2-(4-Methyl-6-oxo-2-phenyl-1,6-dihydro-5-pyrimidinyl)-N-[4-methyl-3-(1-pyrrolidinylmethyl)-2H-chromen-7-yl]acetamide



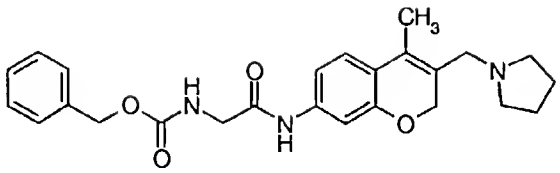
The titled compound was obtained by carrying out the same operation as in Reference Example 1, using 4-methyl-3-(1-pyrrolidinylmethyl)-2H-chromen-7-amine obtained in Reference Example 107.

^{1}H NMR ($CDCl_3$) δ: 1.76 (4H, s), 1.98 (3H, s), 2.49 (4H, s), 2.61 (3H, s), 3.22 (2H, s), 3.65 (2H, s), 4.65 (2H, s), 6.86-7.00 (4H, m), 7.54 (3H, s), 8.01 (2H, s), 8.87 (1H,s).

Melting point: 255-257 ℃ (crystallization solvent: ethyl acetate - n-hexane)

Example 267

Benzyl 2-[[4-methyl-3-(1-pyrrolidinylmethyl)-2H-chromen-7-yl]amino]-2-oxoethylcarbamate



The titled compound was obtained by carrying out the same operation as in Reference Example 1, using 4-methyl-3-(1-pyrrolidinylmethyl)-2H-chromen-7-amine obtained in Reference Example 107.

^{1}H NMR ($CDCl_3$) δ : 1.78 (4H, s), 2.03 (3H, s), 2.53 (4H, s), 3.26 (2H, s), 3.99 (2H, d, J=4.8 Hz), 4.71 (2H, s), 5.17 (2H, s), 5.50 (1H, bs), 7.00-7.14 (4H, m), 7.36 (5H, s), 7.80 (1H, bs).

Melting point : 143-145 ℃ (crystallization solvent : ethyl acetate - n-hexane)

Preparation Example 1

(1) Compound obtained in Reference Example 25	50 mg
(2) Lactose	34 mg
(3) Corn starch	10.6 mg
(4) Corn starch (paste)	5 mg
(5) Magnesium stearate	0.4 mg
(6) Carboxymethylcellulose calcium	20 mg
Total	120 mg

In accordance with a conventional manner, the above (1) to (6) are admixed and tableted using a tableting machine to give tablets.

Preparation Example 2

(1) Compound obtained in Example 1	50 mg
(2) Lactose	34 mg
(3) Corn starch	10.6 mg
(4) Corn starch (paste)	5 mg
(5) Magnesium stearate	0.4 mg
(6) Carboxymethylcellulose calcium	20 mg
Total	120 mg

In accordance with a conventional manner, the above (1) to (6) are admixed and tableted using a tableting machine to give tablets.

Reference Example 1-1

Amplification of rat SLC-1 receptor cDNA by PCR method using rat-brain-originated cDNA

Reverse transcription reaction was done using random primer, with rat-brain-originated poly (A)⁺RNA (Clone Tech Co.) used as a template. Reagent from the TaKaRa RNA PCR ver. 2 kit was used for the reverse transcription reaction. Next, using this reverse transcription product as a template, amplification was done by a PCR method using synthetic DNA primers with sequence numbers 1 and 2. Synthetic DNA primer was constructed to amplify genes in the domain where genes are translated by receptor protein. At that time, individual restriction enzyme recognition sequences were also added on the 5' side and 3' side of the gene, to add a nucleotide sequence on the 5' side of gene which recognized restriction enzyme Sal I, and to add a nucleotide sequence on the 3' side of the gene which recognized the restriction enzyme Spe I. The reactant was constituted of 5 µl of cDNA template, 0.4 µM of synthetic DNA primer, 0.25 mM of dNTPs, 0.5 µl of Pfu (StrataGene Co.) DNA polymerase, and buffers attached to enzymes, with total reaction quantity set at 50 µl.

A thermal cycler (Parkin Elmer Co.) was used to produce cycles for amplification. After heating at 94°C for 60 seconds, the cycle consisting of 94°C for 60 seconds, 60°C for 30 seconds, and 72°C for 150 seconds, was repeated 35 times, and finally reaction was conducted at 72°C for 10 minutes. After 0.8% agarose gel electrophoresis, the amplified products were confirmed by ethidium bromide dying.

Reference Example 1-2

Subcloning of PCR products into plasmid vector, and confirmation of an amplified cDNA sequence by decoding of a nucleotide sequence in an inserted cDNA portion

The reaction product after PCR conducted in Reference Example 1-1 was separated using 0.8% low-melting point agarose gel. After the band section was cut out using a razor, DNA was recovered by conducting fragmentation, phenol extraction, phenol-chloroform extraction and ethanol precipitation. The recovered DNA was subcloned on plasmid vector PCR-Script Amp SK(+) in accordance with prescription of the PCR-Script™ Amp SK(+) cloning kit (Stratagene Co.). After this was introduced into Escherichia coli XL-1 Blue (Stratagene Co.) by transformation, the clones with fragments of inserted cDNA were selected in LB agar culture medium containing ampicillin and X-gal. Only clones showing white color were separated using a sterilized toothpick, and transformant E. coli XL-1 Blue/rat SLC-1 was obtained.

Each clone was cultured overnight in LB culture medium containing ampicillin, and plasmid DNA was prepared using QIA prep8 mini prep (Qiagen). A portion of the prepared DNA was digested with Sal I and Spe I, and the size of the inserted receptor cDNA fragment was confirmed. Reactions to determine nucleotide sequences were carried out using a DyeDeoxy Terminator Cycle Sequence Kit (Parkin Elmer Co.), and decoded using a fluorescent light automatic sequencer. The sequences of the 3 clones obtained were analyzed, and it was confirmed that all of them match the reported gene sequence (Sequence number: 4) in which the Sal I recognition sequence is added on the 5' side and the Spe I recognition sequence is added on the 3' side of the cDNA sequence (Lakaye, B., et al., Biochim. Biophys. Acta, Vol. 1401, pp. 216-220 (1998), accession No. AF08650) coding rat SLC-1 protein (Sequence number: 3).

Reference Example 1-3

Preparation of CHO cells for rat SLC-1 expression

The full-length amino acid sequence of rat brain originated SLC-1, which was confirmed in Reference Example 1-2, was coded, and plasmid was prepared using a plasmid Midi Kit (Qiagen) from the E. coli transformed by the plasmid, to which the gene with Sal I recognition sequence added to the 5' side and Spe I recognition sequence added to the 3' side, had been introduced. Then, the insert section was cut out by digesting with Sal I and Spe I. The insert DNA was cut out with a razor from the agarose gel after electrophoresis.

Next, fragmentation, phenol extraction, phenol-chloroform extraction, and ethanol precipitation, were conducted and the DNA was recovered. This insert DNA was added to vector plasmid pAKKO-111H (the same vector plasmid as pAKKO1.11H described in Hinuma, S., et al., Biochim. Biophys. Acta, Vol. 1219, pp. 251-259 (1994)) for animal cell expression which was digested with Sal I and Spe I, and ligation was conducted using T4 ligase (TaKaRa Shuzo), to construct pAKKO-SLC-1 plasmid for protein expression.

After E. coli DH5 transformed by pAKKO-SLC-1 was cultured, pAKKO-SLC-1 plasmid DNA was prepared using a Plasmid Midi Kit (Qiagen). This was introduced into CHO dhfr$^-$ cells in accordance with the attached protocol, using a CellPhect Transfection Kit (Amersham Pharmacia Biotech Co.). A coprecipitating suspension of 10 μg of DNA and calcium phosphate was prepared, and this suspension was added to 10 cm Petri dishes in which 5×10^5 or 1×10^6 of CHO dhfr$^-$ cells had been seeded 24 hours previously. After these cells were cultured for 1 day in MEMa culture medium containing 10% fetal bovine serum, subculture was conducted, and cultivation was conducted in selective culture medium, MEMa culture medium containing no nucleic acid but containing 10% dialyzed fetal bovine serum. 56 clones of colonies of the transformed CHO cells expressing SLC-1, proliferated in the selective culture medium, were

selected.

Reference Example 1-4

Selection of CHO/SLC-1 cell strain expressing a large quantity of full-length rat SLC-1 receptor protein mRNA

The quantity of expressed full-length rat SLC-1 receptor protein mRNA of 56 clones of the CHO/SLC-1 strains established in Reference Example 1-3, was measured using a Cytostar T Plate (Amersham Pharmacia Biotech Co.) as shown below according to the attached protocol. Each well of the Cytostar T Plate was seeded with each clone of the CHO/SLC-1 strain by 2.5×10^4, and cultured for 24 hours, then the cells were fixed using 10% formalin. After 0.25% Triton X-100 was added to each well to increase cell permeability, ^{35}S-labeled riboprobes with sequence number: 5 were added and hybridized. 20 mg/ml of RNaseA was added to each well to digest free riboprobes. After the plate was thoroughly washed, the radioactivity of the hybridized riboprobes was determined using a Topcounter. Strains with high radioactivity showed large amounts of mRNA expression. In particular, mainly used was Clone number 44 among 3 clones which showed large amounts of mRNA expression.

Reference Example 1-5

Isolation of plasmid containing human SLC-1 cDNA

After nicks were inserted into the DNA of Human fetal brain originated cDNA library (SUPERSCRIPT™ cDNA Library; GIBCOBRL Co.) according to the manual of the Genetrapper cDNA positive selection system (GIBCOBRL Co.), using pharge F1 endonuclease, single stranded human fetal brain originated cDNA library was prepared by digesting the above-mentioned library with Escherichia coli exonuclease III.

Biotin-14-dCTP was added to the 3' end of synthetic oligonucleotide (equivalent to 1434-1451 of accession No. U71092), sequence number: 6 which was prepared according

to the report by Kolakowski Jr., et al. (Kolakowski Jr., et al. (1996) FEBS Lett. Vol. 398, pp. 253-258) using Terminal Deoxynucleotidyl Transferase, and biotinated oligonucleotide was prepared. The above manual was followed regarding composition of a reaction mixture and reaction time.

After 4 µg of single stranded human fetal brain originated cDNA library was kept at 95° C for 1 minute, the library was rapidly cooled on ice. 20 ng of biotinated oligonucleotide was added, which was hybridized using the attached hybridization buffer at 37° C for 1 hour. Streptoavidin beads were added to the mixture, then single stranded human fetal brain originated cDNA hybridized by biotinated oligonucleotide, was isolated using a MAGNA-SEP Magnetic Particle Separator (GIBCOBRL Co.). The complementary strand was synthesized according to the manual, using as primer 50 ng of synthetic oligonucleotide (equivalent to 1011 - 1028 of accession No. U71092) of sequence number: 7, prepared based on the report by Kolakowski Jr., et al (Kolakowski Jr., et al. (1996) FEBS Lett. Vol. 398, pp. 253-258), to give the double stranded plasmid.

Reference Example 1-6

Determination of nucleotide sequence of plasmid containing isolated human SLC-1 cDNA

After the plasmid obtained in Reference Example 1-5 was introduced into ELECTROMAX™DH10B™ Cells by the electroporation method, clones with cDNA inserted fragments were selected in LB agar culture medium containing ampicillin and X-gal. Using a sterilized toothpick, only the clones showing white color were separated to give transformant E. coli DH10B/hSLC-1. Individual clones were cultured overnight in LB culture medium containing ampicillin, and the plasmid DNA was refined using QIA prep8 mini prep (Qiagen). The reactions

to determine nucleotide sequence were conducted using a DyeDeoxy Terminator Cycle Sequence Kit (Parkin Elmer Co.), and the nucleotide sequence was decoded using a fluorescent light automatic sequencer.

As the results, obtained was the sequence shown in Sequence number: 8. The amino acid sequence (Sequence number: 9) coded by the nucleotide sequence obtained here, differs from the human SLC-1 amino acid sequence predicted as the sequence analogized from rat SLC-1 based on human chromosome DNA sequence (accession number: Z86090) containing human SLC-1 sequence, in the report by Lakaye, et al. (Lakaye, B., et al. (1998) Biochim. Biophys. Acta. Vol. 1401, pp. 216-220). This shows the presence of ATG, the initiation codon, on mRNA, in the 69 and 64 amino acids upstream from the estimated sequence. Escherichia coli DH10B/phSLC1L8, the transformant produced by the plasmid containing DNA coding this sequence was deposited at IFO and NIBH.

Reference Example 1-7

Amplification of human SLC-1cDNA by PCR method using human fetal brain originated cDNA

Amplification by the PCR method was conducted using as the template plasmid containing human SLC-1 DNA sequence cloned by the gene trap method, and using synthetic DNA primers of sequence number: 10 and sequence number: 11, and synthetic DNA primers of sequence number: 12 and sequence number: 13, respectively. The former amplified DNA and the latter amplified DNA were named as "human SLC-1(S)" and "human SLC-1(L)", respectively. The synthetic DNA primer was constructed so that the genes in the domain translated to the receptor protein were amplified. At that time, a recognition sequence for each restriction enzyme was added on the 5' side and 3' side, so that the nucleotide sequence recognized by restriction enzyme Sal I would be added on the 5' side of the gene, and the nucleotide sequence

recognized by restriction enzyme Spe I would be added on the 3' side. The composition of the reaction mixture for human SLC-1(S) amplification was: 5 µl of plasmid template containing human SLC-1 DNA sequence, 0.4 µM of respective synthetic DNA primers, 0.2 mM of dNTPs and 0.5 µl of Pfu DNA polymerase and buffers attached to the enzyme, with total quantity for reaction set at 50 µl. A thermal cycler (Parkin Elmer Co.) was used for the cycles for amplification. After heating at 94°C for 60 seconds, the cycle consisting of 94°C for 60 seconds, 57°C for 60 seconds, and 72°C for 150 seconds, was repeated 25 times, and finally the temperature of the reactant was maintained at 72°C for 10 minutes. The composition of the reaction mixture for human SLC-1(L) amplification was 5 µl of plasmid template containing human SLC-1 DNA sequence, 0.4 µM of respective synthetic DNA primers, 0.2 mM of dNTPs, 0.5 µl of Pfu DNA polymerase and buffers attached to the enzymes, with total quantity for reaction set at 50 µl. A thermal cycler (Parkin Elmer Co.) was used for the cycles for amplification. After heating at 94°C for 60 seconds, the cycle consisting of 94°C for 60 seconds, 60°C for 60 seconds, and 72°C for 3 minutes, was repeated 25 times, and finally the temperature of the reactant was maintained at 72°C for 10 minutes. After 0.8% agarose gel electrophoresis, confirmation of amplified products was conducted by ethidium bromide dying.

Reference Example 1-8

Subcloning of PCR product into plasmid vector and confirmation of amplified cDNA sequence by decoding of nucleotide sequence of inserted cDNA section

The reaction product after PCR in Reference Example 1-7 was separated using 0.8% low-melting point agarose gel, and the band section was cut out using a razor. After that, fragmentation, phenol extraction, phenol-chloroform extraction, and ethanol precipitation were conducted, and

the DNA was recovered. The recovered DNA was subcloned into pCR-Script Amp SK(+) plasmid vector, as prescribed by the PCR-Script™ Amp SK(+) cloning kit (Stratagene Co.). After this was introduced into Escherichia coli DH5a competent cells (TOYOBO) and transformed, the clones with cDNA inserted fragments were selected in LB agar culture medium containing ampicillin and X-gal. Using a sterilized toothpick, only clones showing white color were separated to give E. coli DH5α/hSLC-1(S), which is a transformant of human SLC-1 (S), and E. coli DH5α/hSLC-1(L), which is a transformant of human SLC-1 (L). Each clone was cultured overnight in LB culture medium containing ampicillin, and plasmid DNA was prepared using QIA prep8 mini prep (Qiagen). Some of the prepared DNA was digested with Sal I and Spe I restriction enzymes, and the size of the receptor cDNA fragments inserted was confirmed. The reactions to determine nucleotide sequence were conducted using a DyeDeoxy Terminator Cycle Sequence Kit (Parkin Elmer Co.) and the nucleotide sequence was decoded using a fluorescent light automatic sequencer. The sequence of the obtained clones respectively matched the DNA sequence (sequence number:14) which should be amplified by synthetic DNA primers of sequence number: 10 and sequence number: 11 using human SLC-1 gene as a template, and the DNA sequence (sequence number: 15) which should be amplified by synthetic DNA primers of sequence number: 12 and sequence number: 13 using human SLC-1 gene as a template.

Reference Example 1-9

Preparation of CHO cells for expression of human SLC-1(S), and CHO cells for expression of human SLC-1(L)

Plasmid was prepared from the E. coli clones transformed by the plasmid wherein inserted were human SLC-1(S) and human SLC-1(L) whose sequences were confirmed in Reference Example 1-8, using a Plasmid Midi Kit (Qiagen), and the insert section was cut out using Sal I and Spe I

restriction enzymes. After electrophoresis was conducted, the insert DNA was cut out from agarose gel using a razor. Next, fragmentation, phenol extraction, phenol-chloroform extraction, and ethanol precipitation were conducted, and the insert DNA was recovered.

This insert DNA was added to pAKKO-111H vector plasmid for animal cell expression, digested with Sal I and Spe I (the same vector plasmid as the pAKKO1.11H described in Hinuma, S., et al., Biochim. Biophys. Acta, Vol. 1219, pp. 251-259 (1994)), and ligation was conducted by adding T4 ligase (TaKaRa Shuzo), to construct pAKKO-hSLC-1(S) and pAKKO-hSLC-1(L) plasmids for protein expression.

After E. coli DH5α (TOYOBO) transformed by pAKKO-hSLC-1(S) and pAKKO-hSLC-1(L) was cultured, pAKKO-hSLC-1(S) and pAKKO-hSLC-1(L) plasmid DNAs were prepared using a Plasmid Midi Kit (Qiagen). These were introduced into CHO dhfr$^-$ cells in accordance with the attached protocol, using a CellPhect Transfection Kit (Amersham Pharmacia Biotech Co.). A coprecipitative suspension of 10 μg of DNA with calcium phosphate was made, which was added to 10 cm Petri dishes seeded 24 hours in advance with 5×10^5 or 1×10^6 CHO dhfr$^-$ cells. After the above was cultured for 1 day in MEMa culture medium containing 10% fetal bovine serum, subculture was conducted, and then cultivation was conducted in MEMα culture medium containing no nucleic acid but containing 10% dialyzed fetal bovine serum, which is a selective culture medium. 56 clones of colonies of transformed cells which are human SLC-1(S) gene introduced CHO cells, and 61 clones of colonies of transformed cells which are human SLC-1(L) gene introduced CHO cells, both of which proliferated in the selective culture medium, were selected.

Reference Example 1-10

Selection of cell colonies into which genes with large quantities of human SLC-1(S) and human SLC-1 (L) mRNA

expression have been introduced

The quantities of expressed mRNA of 56 clones of CHO/hSLC-1(S) colonies and 61 clones of CHO/hSLC-1(L) colonies, both of which were established in Reference Example 1-9, were measured in accordance with the attached protocol using a Cytostar T Plate (Amersham Pharmacia Biotech Co.) as shown below.

After each well of the Cytostar T Plate was seeded with each clone of CHO/hSLC-1(S) colonies and CHO/hSLC-1(L) colonies by 2.5×10^4, and cultured for 24 hours, the cells were fixed using 10% formalin.

After 0.25% Triton X-100 was added to each well to increase cell permeability, ^{35}S-labeled riboprobe of sequence number: 16 was added and hybridization was conducted.

20 mg/ml of RNaseA was added to each well to digest free riboprobe. After the plate was washed well, the radioactivity of the hybridized riboprobe was determined. Colonies showing high radioactivity expressed large quantities of mRNA. Of the 7 clones which expressed large quantities of mRNA, mainly used was Clone number 57.

Experimental Example 1

Determination of antagonist activity using GTPgS binding assay of test compound

Membrane fraction was prepared by the following method, using the human SLC-1 expressing CHO cell clone 57 obtained in Reference Example 1-10, and the rat SLC-1 expressing CHO cell clone 44 obtained in Reference Example 1-4.

The human and rat SLC-1 expressing CHO cells (1×10^8) were scraped in buffer saline phosphate (pH 7.4) to which 5 mM EDTA (ethylenediaminetetraacetic acid) had been added, and centrifuged. 10 ml of homogenized buffer (10 mM $NaHCO_3$, 5 mM EDTA, pH 7.5) was added to the cell pellets, and they were homogenized using a Polytron homogenizer. The

supernatant obtained by centrifugation at 400 × g for 15 minutes was further centrifuged at 100,000 × g for 1 hour, to obtain the membrane fraction precipitate. This precipitate was suspended in 2 ml of assay buffer [50 mM Tris-HCl(pH 7.5), 1 mM EDTA, 0.1% BSA (bovine serum albumin), 10 mM $MgCl_2$, 100 mM NaCl, 1 μM GDP (guanosine 5'-diphosphate), 0.25 mM PMSF (phenylmethylsulfonyl fluoride), 1 mg/ml pepstatin, 20 mg/ml leupeptin, 10 mg/ml phosphoramidon], which was centrifuged at 100,000 × g for 1 hour. The membrane fraction recovered as precipitate was suspended again in 2 ml of assay buffer, and after the suspension was divided, individual portions were preserved at -80° C and thawed before every use.

Determination of antagonist activity of the test compound was conducted as shown below. After 171 μl of SLC-1 expressing CHO cell membrane fractions diluted with assay buffer was poured into each well of a 96-well polypropylene plate, 2 μl of $3x10^{-10}$M MCH diluted with DMSO solution, 2 μl of test compound solution diluted to various concentrations, and 25 μl of [^{35}S]-Guanosine 5'-(γ-thio) triphosphate (produced by Daiichi Kagaku Yakuhin) were added respectively. (Final concentration of cell membrane: 20 μg/ml, final concentration of [^{35}S]-Guanosine 5'-(γ-thio) triphosphate: 0.33 nM).

After this reaction mixture was allowed to react for 1 hour under stirring, it was filtered under vacuum using a glass filter (GF-C), then the filter was washed 3 times with 300 μl of washing solution (50 mM Tris-HCl buffer solution pH 7.5). 50 ml of liquid scintillator was added to the glass filter, and residual radioactivity was determined using a liquid scintillation counter.

The IC_{50} value of the compound was calculated from the binding inhibition rate (%), based on the definition that the binding inhibition rate (%) = (radioactivity when compound and MCH were added - radioactivity when DMSO solution was added)/(radioactivity when MCH was added -

radioactivity when DMSO solution was added) × 100.

The results were shown below.

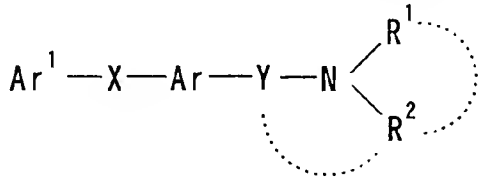
Compound Number	Inhibition Activity (IC_{50} value: nM)
Reference Example 25	90
Example 1	40

Industrial Applicability

Compounds (I), (I') and salts thereof possess excellent MCH receptor antagonistic activities, and are useful as an agent for preventing or treating obesity, etc.

CLAIMS

1. A melanin-concentrating hormone antagonist which comprises a compound of the formula :



(I)

wherein Ar^1 is a cyclic group which may have substituents;
X is a spacer having a main chain of 1 to 6 atoms;
Y is a bond or a spacer having a main chain of 1 to 6 atoms;
Ar is a monocyclic aromatic ring which may be condensed with a 4 to 8 membered non-aromatic ring, and may have further substituents;
R^1 and R^2 are independently hydrogen atom or a hydrocarbon group which may have substituents; R^1 and R^2, together with the adjacent nitrogen atom, may form a nitrogen-containing hetero ring which may have substituents; R^2 may form a spiro ring together with Ar; or R^2, together with the adjacent nitrogen atom and Y, may form a nitrogen-containing hetero ring which may have substituents; or a salt thereof.

2. An antagonist according to claim 1, wherein Y is a spacer having a main chain of 1 to 6 atoms; R^1 and R^2 are independently hydrogen atom or a hydrocarbon group which may have substituents; R^1 and R^2, together with the adjacent nitrogen atom, may form a nitrogen-containing hetero ring which may have substituents; or R^2 may form a spiro ring together with Ar.

3. An antagonist according to claim 2, wherein Ar^1 is an aromatic group which may have substituents; and "a hydrocarbon group which may have substituents" for R^1 and R^2 is "C_{1-6} alkyl which may have substituents".

4. An antagonist according to claim 1, wherein the cyclic

group for Ar^1 is C_{6-14} monocyclic or condensed polycyclic aromatic hydrocarbon group.

5. An antagonist according to claim 1, wherein the cyclic group for Ar^1 is a group formed by removing an optional one hydrogen atom from an aromatic ring assemble in which 2 or 3 C_{6-14} monocyclic or condensed polycyclic aromatic hydrocarbon groups are directly bonded by single bonds.

6. An antagonist according to claim 1, wherein the cyclic group for Ar^1 is a group formed by removing an optional one hydrogen atom from an aromatic ring assemble in which C_{6-14} monocyclic or condensed polycyclic aromatic hydrocarbon and 5 to 10 membered aromatic hetero ring are directly bonded by a single bond.

7. An antagonist according to claim 1, wherein Ar^1 is phenyl, biphenylyl, phenyl-pyridyl, phenyl-furyl, phenyl-isoxazolyl, diphenyl-oxazolyl, pyridyl-phenyl, phenyl-pyrimidinyl, benzofuranyl-phenyl, furyl-phenyl, terphenyl, thienyl-phenyl, indolyl, naphthyl-oxadiazolyl, benzofuranyl-oxadiazolyl, benzothienyl, benzofuranyl, fluorenyl, pyridyl-pyrrolyl or thioxanthenyl;
each of which may have 1 to 3 substituents selected from the group consisting of halogen atom; nitro; C_{1-3} alkylenedioxy; optionally halogenated C_{1-6} alkyl; hydroxy-C_{1-6} alkyl; optionally halogenated C_{3-6} cycloalkyl; optionally halogenated C_{1-6} alkoxy; optionally halogenated C_{1-6} alkythio; hydroxy; C_{7-19} aralkyloxy which may have substituents; C_{6-14} aryloxy which may have substituents; amino; mono-C_{1-6} alkylamino; di-C_{1-6} alkylamino; 5 to 7 membered saturated cyclic amino which may have substituents and may be condensed with a benzene ring; 5 to 7 membered non-aromatic heterocyclic groups which may have substituents; formyl; carboxy; C_{6-14} aryl-carbonyl which may

have substituents; C_{6-14} aryl-carbamoyl which may have substituents; aromatic hetero ring-carbamoyl which may have substituents; C_{1-6} alkoxy-carbonyl; optionally halogenated C_{1-6} alkyl-carboxamide; C_{6-14} aryl-carboxamide which may have substituents; C_{7-19} aralkyl-carboxamide which may have substituents; aromatic hetero ring-carboxamide which may have substituents; N-(C_{6-14} aryl-carbonyl which may have substituents)-N-C_{1-6} alkylamino; C_{6-14} arylamino-carbonylamino which may have substituents; C_{6-14} arylsulfonylamino which may have substituents; C_{6-14} aryl-carbonyloxy which may have substituents; oxo; carboxy-C_{1-6} alkyl; C_{1-6} alkoxy-carbonyl-C_{1-6} alkyl; C_{7-19} aralkyl which may have substituents; aromatic hetero ring-C_{1-6} alkoxy; and cyano.

8. An antagonist according to claim 1, wherein Ar^1 is piperidinyl, piperazinyl, pyrrolidinyl, dihydropyridyl or tetrahydropyridyl; each of which may have 1 or 2 substituents selected from the group consisting of oxo, C_{6-14} aryl which may have substituents, hydroxy, C_{7-19} aralkyloxy-carbonyl, and C_{7-19} aralkyl.

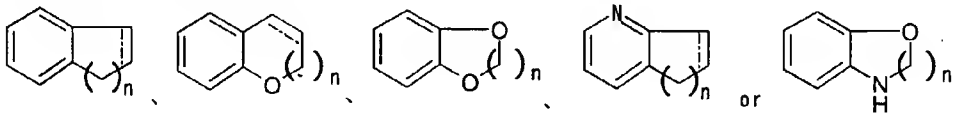
9. An antagonist according to claim 1, wherein the "spacer having a main chain of 1 to 6 atoms" for X and Y is a bivalent group consisting of 1 to 3 species selected from -O-, -S-, -CO-, -SO-, $-SO_2-$, $-NR^8-$ (R^8 is hydrogen atom, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{1-6} alkyl-carbonyl, optionally halogenated C_{1-6} alkylsulfonyl), and a bivalent C_{1-6} non-cyclic hydrocarbon group which may have substituents.

10. An antagonist according to claim 1, wherein X is $-CONR^{8c}-$, $-NR^{8c}CO-$, $-CH=CH-CONR^{8c}-$ or $-SO_2NR^{8c}-$ wherein R^{8c} is hydrogen atom or C_{1-6} alkyl.

11. An antagonist according to claim 1, wherein Y is an

optionally halogenated bivalent C_{1-6} non-cyclic hydrocarbon group.

12. An antagonist according to claim 1, wherein Ar is a ring of the formula :



wherein ----- is a single bond or double bond, n is an integer of 1 to 4.

13. An antagonist according to claim 1, wherein R^1 and R^2 are hydrogen atom or C_{1-6} alkyl which may have substituents; or R^1 and R^2, together with the adjacent nitrogen atom, form a 3 to 8 membered nitrogen-containing hetero ring.

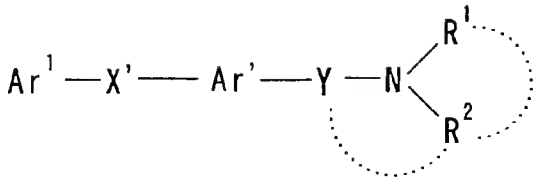
14. An antagonist according to claim 1, which is an agent for preventing or treating diseases caused by a melanin-concentrating hormone.

15. An antagonist according to claim 1, which is an agent for preventing or treating obesity.

16. An antagonist according to claim 1, which is an anorectic agent.

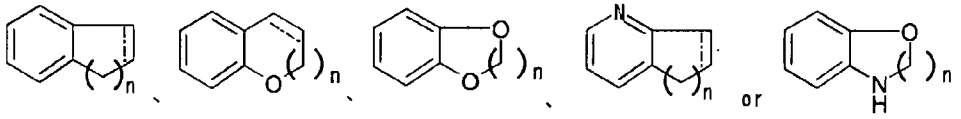
17. A pharmaceutical, which comprises a melanin-concentrating hormone antagonist in combination with at least one species selected from the group consisting of an agent for treating diabetes, an agent for treating hypertension and an agent for treating arteriosclerosis.

18. A compound of the formula :

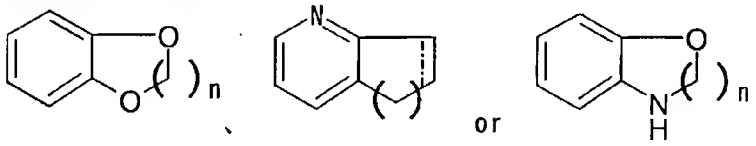


(I')

wherein Ar^1 is a cyclic group which may have substituents;
Ar' is a ring of the formula :

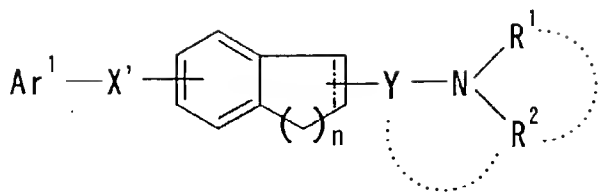


wherein ----- is a single bond or double bond, n is an integer of 1 to 4, and each ring may have substituents;
X' is $-CONR^{8c}-$, $-NR^{8c}CO-$, $-CH=CH-CONR^{8c}-$ or $-SO_2NR^{8c}-$ where R^{8c} is hydrogen atom or C_{1-6} alkyl;
Y is a spacer having a main chain of 1 to 6 atoms;
R^1 and R^2 are independently hydrogen atom or a hydrocarbon group which may have substituents; R^1 and R^2, together with the adjacent nitrogen atom, may form a nitrogen-containing hetero ring which may have substituents; or R^2, together with the adjacent nitrogen atom and Y, may form a nitrogen-containing hetero ring which may have substituents;
provided that Ar' is a ring of the formula :



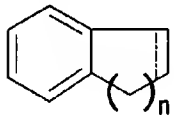
wherein symbols have the same meanings as defined above, and each ring may have substituents, when X' is $-SO_2NH-$; and provided that Ar^1 is not biphenylyl which may be substituted, when X' is -CONH- and Ar' is any one of benzopyran, dihydrobenzopyran, dihyrobenzoxazine, dihydrobenzoxazole or tetrahydrobenzoxazepine; (excluding N-[2-(N,N-dimethylamino)methyl-6-tetralinyl]-4-biphenylylcarboxamide); or a salt thereof.

19. A compound of the formula :



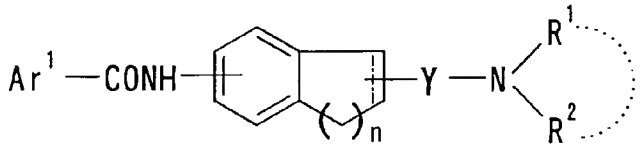
(I'-1)

wherein Ar^1 is a cyclic group which may have substituents;
----- is a single bond or double bond;
n is an integer of 1 to 4;
X' is $-CONR^{8c}-$, $-NR^{8c}CO-$ or $-CH=CH-CONR^{8c}-$ where R^{8c} is hydrogen atom or C_{1-6} alkyl;
Y is a spacer having a main chain of 1 to 6 atoms;
R^1 and R^2 are independently hydrogen atom or a hydrocarbon group which may have substituents; R^1 and R^2, together with the adjacent nitrogen atom, may form a nitrogen-containing hetero ring which may have substituents; or R^2, together with the adjacent nitrogen atom and Y, may form a nitrogen-containing hetero ring which may have substituents;
a ring of the formula :



wherein symbols have the same meanings as defined above, may have further substituents;
provided that N-[2-(N,N-dimethylamino)methyl-6-tetralinyl]-4-biphenylylcarboxamide is excluded; or a salt thereof.

20. A compound according to claim 19, which is of the formula :



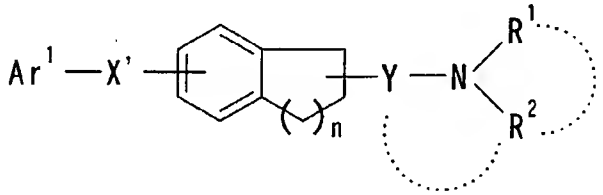
(I'-2)

wherein R^1 and R^2 are independently hydrogen atom or a hydrocarbon group which may have substituents; R^1 and R^2,

together with the adjacent nitrogen atom, may form a nitrogen-containing hetero ring which may have substituents; the other symbols have the same meanings as defined in claim 19.

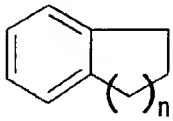
21. A compound according to claim 20, wherein Ar^1 is an aromatic group which may have substituents; and "a hydrocarbon group which may have substituents" for R^1 and R^2 is "C_{1-6} alkyl which may have substituents".

22. A compound of the formula :



(I'-3)

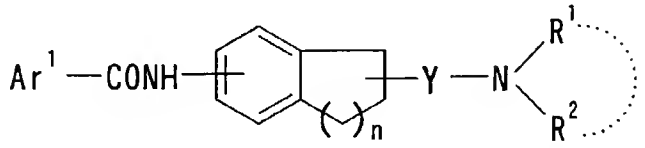
wherein Ar^1 is a cyclic group which may have substituents;
n is an integer of 1 to 4;
X' is $-CONR^{8c}-$, $-NR^{8c}CO-$ or $-CH=CH-CONR^{8c}-$ where R^{8c} is hydrogen atom or C_{1-6} alkyl;
Y is a spacer having a main chain of 1 to 6 atoms;
R^1 and R^2 are independently hydrogen atom or a hydrocarbon group which may have substituents; R^1 and R^2, together with the adjacent nitrogen atom, may form a nitrogen-containing hetero ring which may have substituents; or R^2, together with the adjacent nitrogen atom and Y, may form a nitrogen-containing hetero ring which may have substituents;
a ring of the formula :



wherein n has the same meaning as defined above, may have further substituents;
provided that N-[2-(N,N-dimethylamino)methyl-6-tetralinyl]-4-biphenylylcarboxamide is excluded; or a salt

thereof.

23. A compound according to claim 22, which is of the formula :

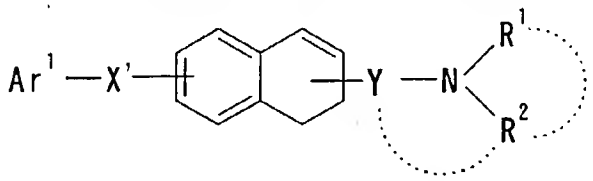


(I'-4)

wherein R^1 and R^2 are independently hydrogen atom or a hydrocarbon group which may have substituents; R^1 and R^2, together with the adjacent nitrogen atom, may form a nitrogen-containing hetero ring which may have substituents; the other symbols have the same meanings as defined in claim 22.

24. A compound according to claim 23, wherein Ar^1 is an aromatic group which may have substituents; and "a hydrocarbon group which may have substituents" for R^1 and R^2 is "C_{1-6} alkyl which may have substituents".

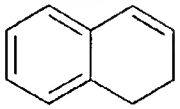
25. A compound of the formula :



(I'-5)

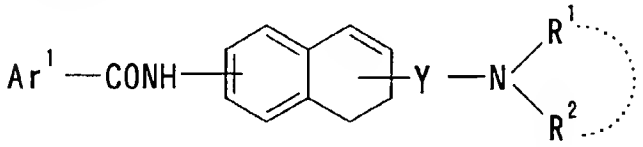
wherein Ar^1 is a cyclic group which may have substituents;
X' is $-CONR^{8c}-$, $-NR^{8c}CO-$ or $-CH=CH-CONR^{8c}-$ where R^{8c} is hydrogen atom or C_{1-6} alkyl;
Y is a spacer having a main chain of 1 to 6 atoms;
R^1 and R^2 are independently hydrogen atom or a hydrocarbon group which may have substituents; R^1 and R^2, together with the adjacent nitrogen atom, may form a nitrogen-containing hetero ring which may have substituents; or R^2, together with the adjacent nitrogen atom and Y, may form a nitrogen-containing hetero ring which may have substituents;

a ring of the formula :



may have further substituents; or a salt thereof.

26. A compound according to claim 25, which is of the formula :

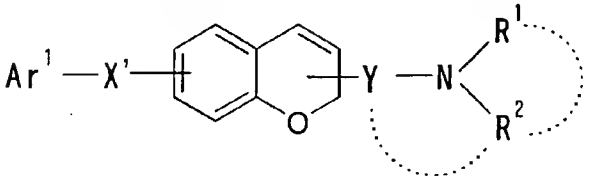


(I'-6)

wherein R^1 and R^2 are independently hydrogen atom or a hydrocarbon group which may have substituents; R^1 and R^2, together with the adjacent nitrogen atom, may form a nitrogen-containing hetero ring which may have substituents; the other symbols have the same meanings as defined in claim 25.

27. A compound according to claim 26, wherein Ar^1 is an aromatic group which may have substituents; and "a hydrocarbon group which may have substituents" for R^1 and R^2 is "C_{1-6} alkyl which may have substituents".

28. A compound of the formula :

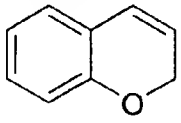


(I'-7)

wherein Ar^1 is a cyclic group which may have substituents;
X' is $-CONR^{8c}-$, $-NR^{8c}CO-$, $-CH=CH-CONR^{8c}-$ or $-SO_2NR^{8c}-$ where R^{8c} is hydrogen atom or C_{1-6} alkyl;
Y is a spacer having a main chain of 1 to 6 atoms;
R^1 and R^2 are independently hydrogen atom or a hydrocarbon group which may have substituents; R^1 and R^2, together with the adjacent nitrogen atom, may form a nitrogen-containing

hetero ring which may have substituents; or R^2, together with the adjacent nitrogen atom and Y, may form a nitrogen-containing hetero ring which may have substituents;

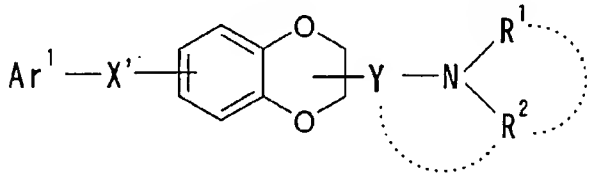
a ring of the formula :



may have further substituents;

provided that Ar^1 is not biphenylyl which may be substituted, when X' is -CONH-; or a salt thereof.

29. A compound of the formula :



(I'-8)

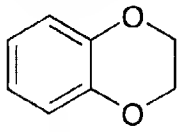
wherein Ar^1 is a cyclic group which may have substituents;

X' is $-CONR^{8c}-$, $-NR^{8c}CO-$, $-CH=CH-CONR^{8c}-$ or $-SO_2NR^{8c}-$ where R^{8c} is hydrogen atom or C_{1-6} alkyl;

Y is a spacer having a main chain of 1 to 6 atoms;

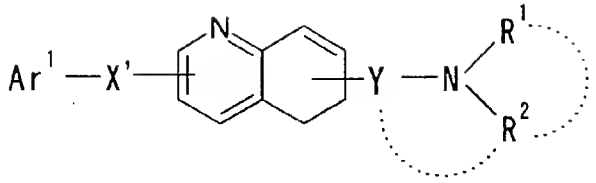
R^1 and R^2 are independently hydrogen atom or a hydrocarbon group which may have substituents; R^1 and R^2, together with the adjacent nitrogen atom, may form a nitrogen-containing hetero ring which may have substituents; or R^2, together with the adjacent nitrogen atom and Y, may form a nitrogen-containing hetero ring which may have substituents;

a ring of the formula :



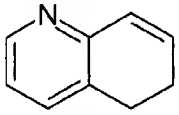
may have further substituents; or a salt thereof.

30. A compound of the formula :



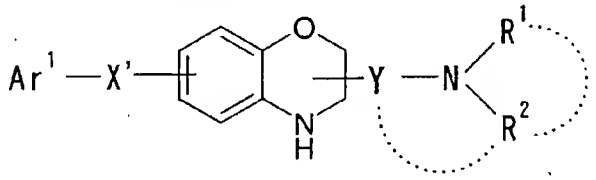
(I'-9)

wherein Ar^1 is a cyclic group which may have substituents;
X' is $-CONR^{8c}-$, $-NR^{8c}CO-$, $-CH=CH-CONR^{8c}-$ or $-SO_2NR^{8c}-$ where R^{8c} is hydrogen atom or C_{1-6} alkyl;
Y is a spacer having a main chain of 1 to 6 atoms;
R^1 and R^2 are independently hydrogen atom or a hydrocarbon group which may have substituents; R^1 and R^2, together with the adjacent nitrogen atom, may form a nitrogen-containing hetero ring which may have substituents; or R^2, together with the adjacent nitrogen atom and Y, may form a nitrogen-containing hetero ring which may have substituents;
a ring of the formula :



may have further substituents; or a salt thereof.

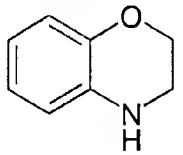
31. A compound of the formula :



(I'-10)

wherein Ar^1 is a cyclic group which may have substituents;
X' is $-CONR^{8c}-$, $-NR^{8c}CO-$, $-CH=CH-CONR^{8c}-$ or $-SO_2NR^{8c}-$ where R^{8c} is hydrogen atom or C_{1-6} alkyl;
Y is a spacer having a main chain of 1 to 6 atoms;
R^1 and R^2 are independently hydrogen atom or a hydrocarbon group which may have substituents; R^1 and R^2, together with the adjacent nitrogen atom, may form a nitrogen-containing hetero ring which may have substituents; or R^2, together with the adjacent nitrogen atom and Y, may form a nitrogen-containing hetero ring which may have

substituents;
a ring of the formula :



may have further substituents;
provided that Ar^1 is not biphenylyl which may be substituted, when X' is -CONH-; or a salt thereof.

32. A pharmaceutical composition which comprises a compound as defined in any one of claims 18, 19, 22, 25, 26, 28, 29, 30 and 31.

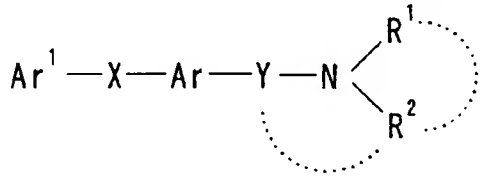
33. A prodrug of a compound as defined in any one of claims 18, 19, 22, 25, 26, 28, 29, 30 and 31.

34. A compound according to claim 18, which is
N-[2-(N,N-dimethylamino)methyl-6-tetralinyl]-(4'-methoxybiphenyl-4-yl)carboxamide;
4'-fluoro-N-[6-[(N,N-dimethylamino)methyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide;
4'-fluoro-N-[6-(1-piperidinylmethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]4-carboxamide;
4'-fluoro-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide;
(+)-4'-fluoro-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide;
(-)-4'-fluoro-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide;
4'-chloro-N-[3-[(N,N-dimethylamino)methyl]-2H-chromen-7-yl][1,1'-biphenyl]-4-carboxamide;
4'-fluoro-N-[6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-

naphthalenyl][1,1'-biphenyl]-4-carboxamide;
N-[3-[(dimethylamino)methyl]-2H-chromen-7-yl]-4'-fluoro[1,1'-biphenyl]-4-carboxamide;
4'-chloro-N-[6-[(dimethylamino)methyl]-5-methyl-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide;
6-(4-methoxyphenyl)-N-[5-methyl-6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl]nicotinamide;
4'-chloro-N-[7-[(dimethylamino)methyl]-5,6-dihydro-3-quinolinyl][1,1'-biphenyl]-4-carboxamide;
4-(4-chlorophenyl)-N-[6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl]-3,6-dihydro-1(2H)-pyridinecarboxamide;
N-[6-[(dimethylamino)methyl]-7,8-dihydro-2-naphthalenyl]-4-(4-fluorophenyl)-1-piperidinecarboxamide;
4-(4-methoxyphenyl)-N-[6-(1-pyrrolidinylmethyl)-5-methyl-7,8-dihydro-2-naphthalenyl]-1-piperidinecarboxamide;
4'-fluoro-N-[6-[2-(1-pyrrolidinyl)ethyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide;
4'-chloro-N-[6-[2-(1-pyrrolidinyl)ethyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide;
4'-chloro-N-[2-[(dimethylamino)methyl]-3,4-dihydro-2H-1,4-benzoxazin-6-yl][1,1'-biphenyl]-4-carboxamide;
4-(4-methoxyphenyl)-N-[5-methyl-6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl]-1-piperidinecarboxamide;
4-(4-chlorophenyl)-N-[6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenyl]-1-piperidinecarboxamide;
4'-chloro-N-[2-[(dimethylamino)methyl]-1H-inden-6-yl][1,1'-biphenyl]-4-carboxamide;
4'-fluoro-N-[2-(1-pyrrolidinylmethyl)-3,4-dihydro-2H-1,4-benzoxazin-6-yl][1,1'-biphenyl]-4-carboxamide;
4'-fluoro-N-[5-methyl-6-[(4-methyl-1-

piperazinyl)methyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide;
4'-chloro-N-[5-methyl-6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide; or
4-(4-chlorophenyl)-N-[5-methyl-6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenyl]-1-piperidinecarboxamide.

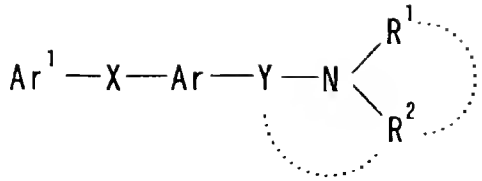
35. A method for preventing or treating diseases caused by a melanin-concentrating hormone in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound of the formula :



(I)

wherein Ar^1 is a cyclic group which may have substituents;
X is a spacer having a main chain of 1 to 6 atoms;
Y is a bond or a spacer having a main chain of 1 to 6 atoms;
Ar is a monocyclic aromatic ring which may be condensed with a 4 to 8 membered non-aromatic ring, and may have further substituents;
R^1 and R^2 are independently hydrogen atom or a hydrocarbon group which may have substituents; R^1 and R^2, together with the adjacent nitrogen atom, may form a nitrogen-containing hetero ring which may have substituents; R^2 may form a spiro ring together with Ar; or R^2, together with the adjacent nitrogen atom and Y, may form a nitrogen-containing hetero ring which may have substituents; or a salt thereof.

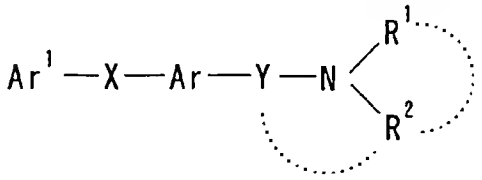
36. A method for preventing or treating obesity in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound of the formula :



(I)

wherein Ar^1 is a cyclic group which may have substituents;
X is a spacer having a main chain of 1 to 6 atoms;
Y is a bond or a spacer having a main chain of 1 to 6 atoms;
Ar is a monocyclic aromatic ring which may be condensed with a 4 to 8 membered non-aromatic ring, and may have further substituents;
R^1 and R^2 are independently hydrogen atom or a hydrocarbon group which may have substituents; R^1 and R^2, together with the adjacent nitrogen atom, may form a nitrogen-containing hetero ring which may have substituents; R^2 may form a spiro ring together with Ar; or R^2, together with the adjacent nitrogen atom and Y, may form a nitrogen-containing hetero ring which may have substituents; or a salt thereof.

37. Use of a compound of the formula :

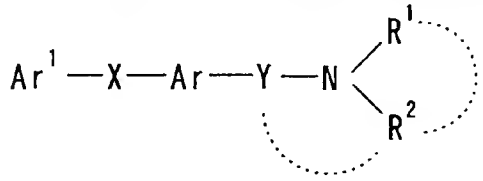


(I)

wherein Ar^1 is a cyclic group which may have substituents;
X is a spacer having a main chain of 1 to 6 atoms;
Y is a bond or a spacer having a main chain of 1 to 6 atoms;
Ar is a monocyclic aromatic ring which may be condensed with a 4 to 8 membered non-aromatic ring, and may have further substituents;
R^1 and R^2 are independently hydrogen atom or a hydrocarbon group which may have substituents; R^1 and R^2, together with the adjacent nitrogen atom, may form a nitrogen-containing hetero ring which may have substituents; R^2 may form a spiro ring together with Ar; or R^2, together with the adjacent nitrogen atom and Y, may form a nitrogen-containing hetero ring which may have substituents; or a salt thereof;

for the manufacture of a pharmaceutical preparation for preventing or treating diseases caused by a melanin-concentrating hormone.

38. Use of a compound of the formula :



(I)

wherein Ar^1 is a cyclic group which may have substituents;
X is a spacer having a main chain of 1 to 6 atoms;
Y is a bond or a spacer having a main chain of 1 to 6 atoms;
Ar is a monocyclic aromatic ring which may be condensed with a 4 to 8 membered non-aromatic ring, and may have further substituents;
R^1 and R^2 are independently hydrogen atom or a hydrocarbon group which may have substituents; R^1 and R^2, together with the adjacent nitrogen atom, may form a nitrogen-containing hetero ring which may have substituents; R^2 may form a spiro ring together with Ar; or R^2, together with the adjacent nitrogen atom and Y, may form a nitrogen-containing hetero ring which may have substituents; or a salt thereof;
for the manufacture of a pharmaceutical preparation for preventing or treating obesity.

SEQUENCE LISTING

<110> Takeda Chemical Industries, Ltd.

<120> Melanin Concentrating Hormone Antagonist

<130> 2648WOOP

<150> JP 11-266298

<151> 1999-09-20

<150> JP 11-357889

<151> 1999-12-16

<150> JP 2000-126272

<151> 2000-04-20

<160> 16

<210> 1

<211> 32

<212> DNA

<213> Artificial Sequence

<220>

<223>

<400> 1

GTCGACATGG ATCTGCAAAC CTCGTTGCTG TG 32

<210> 2

<211> 32

<212> DNA

<213> Artificial Sequence

<220>

<223>

<400> 2

ACTAGTTCAG GTGCCTTTGC TTTCTGTCCT CT 32

<210> 3

<211> 353

<212> PRT

<213> Rat

<400> 3

Met Asp Leu Gln Thr Ser Leu Leu Ser Thr Gly Pro Asn Ala Ser Asn
1 5 10 15

Ile Ser Asp Gly Gln Asp Asn Leu Thr Leu Pro Gly Ser Pro Pro Arg
20 25 30

Thr Gly Ser Val Ser Tyr Ile Asn Ile Ile Met Pro Ser Val Phe Gly
35 40 45

Thr Ile Cys Leu Leu Gly Ile Val Gly Asn Ser Thr Val Ile Phe Ala
50 55 60

Val Val Lys Lys Ser Lys Leu His Trp Cys Ser Asn Val Pro Asp Ile
65 70 75 80

Phe Ile Ile Asn Leu Ser Val Val Asp Leu Leu Phe Leu Leu Gly Met
85 90 95

Pro Phe Met Ile His Gln Leu Met Gly Asn Gly Val Trp His Phe Gly
100 105 110

Glu Thr Met Cys Thr Leu Ile Thr Ala Met Asp Ala Asn Ser Gln Phe
115 120 125

Thr Ser Thr Tyr Ile Leu Thr Ala Met Thr Ile Asp Arg Tyr Leu Ala
130 135 140

Thr Val His Pro Ile Ser Ser Thr Lys Phe Arg Lys Pro Ser Met Ala
145 150 155 160

Thr Leu Val Ile Cys Leu Leu Trp Ala Leu Ser Phe Ile Ser Ile Thr
165 170 175

Pro Val Trp Leu Tyr Ala Arg Leu Ile Pro Phe Pro Gly Gly Ala Val
180 185 190

Gly Cys Gly Ile Arg Leu Pro Asn Pro Asp Thr Asp Leu Tyr Trp Phe

195 200 205

Thr Leu Tyr Gln Phe Phe Leu Ala Phe Ala Leu Pro Phe Val Val Ile

210 215 220

Thr Ala Ala Tyr Val Lys Ile Leu Gln Arg Met Thr Ser Ser Val Ala

225 230 235 240

Pro Ala Ser Gln Arg Ser Ile Arg Leu Arg Thr Lys Arg Val Thr Arg

245 250 255

Thr Ala Ile Ala Ile Cys Leu Val Phe Phe Val Cys Trp Ala Pro Tyr

260 265 270

Tyr Val Leu Gln Leu Thr Gln Leu Ser Ile Ser Arg Pro Thr Leu Thr

275 280 285

Phe Val Tyr Leu Tyr Asn Ala Ala Ile Ser Leu Gly Tyr Ala Asn Ser

290 295 300

Cys Leu Asn Pro Phe Val Tyr Ile Val Leu Cys Glu Thr Phe Arg Lys

305 310 315 320

Arg Leu Val Leu Ser Val Lys Pro Ala Ala Gln Gly Gln Leu Arg Thr

325 330 335

Val Ser Asn Ala Gln Thr Ala Asp Glu Glu Arg Thr Glu Ser Lys Gly

340 345 350

Thr

<210> 4

<211> 1074

<212> DNA

<213> Rat

<400> 4

GTCGACATGG ATCTGCAAAC CTCGTTGCTG TCCACTGGCC CCAATGCCAG CAACATCTCC 60

GATGGCCAGG ATAATCTCAC ATTGCCGGGG TCACCTCCTC GCACAGGGAG TGTCTCCTAC 120

ATCAACATCA TTATGCCTTC CGTGTTTGGT ACCATCTGTC TCCTGGGCAT CGTGGGAAAC 180

TCCACGGTCA TCTTTGCTGT GGTGAAGAAG TCCAAGCTAC ACTGGTGCAG CAACGTCCCC 240

GACATCTTCA TCATCAACCT CTCTGTGGTG GATCTGCTCT TCCTGCTGGG CATGCCTTTC 300

ATGATCCACC AGCTCATGGG GAACGGCGTC TGGCACTTTG GGGAAACCAT GTGCACCCTC 360

ATCACAGCCA TGGACGCCAA CAGTCAGTTC ACTAGCACCT ACATCCTGAC TGCCATGACC 420

ATTGACCGCT ACTTGGCCAC CGTCCACCCC ATCTCCTCCA CCAAGTTCCG GAAGCCCTCC 480

ATGGCCACCC TGGTGATCTG CCTCCTGTGG GCGCTCTCCT TCATCAGTAT CACCCCTGTG 540

TGGCTCTACG CCAGGCTCAT TCCCTTCCCA GGGGGTGCTG TGGGCTGTGG CATCCGCCTG 600

CCAAACCCGG ACACTGACCT CTACTGGTTC ACTCTGTACC AGTTTTTCCT GGCCTTTGCC 660

CTTCCGTTTG TGGTCATTAC CGCCGCATAC GTGAAAATAC TACAGCGCAT GACGTCTTCG 720

GTGGCCCCAG CCTCCCAACG CAGCATCCGG CTTCGGACAA AGAGGGTGAC CCGCACGGCC 780

ATTGCCATCT GTCTGGTCTT CTTTGTGTGC TGGGCACCCT ACTATGTGCT GCAGCTGACC 840

CAGCTGTCCA TCAGCCGCCC GACCCTCACG TTTGTCTACT TGTACAACGC GGCCATCAGC 900

TTGGGCTATG CTAACAGCTG CCTGAACCCC TTTGTGTACA TAGTGCTCTG TGAGACCTTT 960

CGAAAACGCT TGGTGTTGTC AGTGAAGCCT GCAGCCCAGG GGCAGCTCCG CACGGTCAGC 1020

AACGCTCAGA CAGCTGATGA GGAGAGGACA GAAAGCAAAG GCACCTGAAC TAGT 1074

<210> 5

<211> 262

<212> RNA

<213> Rat

<400> 5

GCGAAUUGGG UACCGGGCCC CCCCUCGAGG UCGACGGUAU CGAUAAGCUU GAUAUCGAAU 60

UCCUGCAGCC CGGGGGAUCC GCCCACUAGU UCAGGUGCCU UUGCUUUCUG UCCUCUCCUC 120

AUCAGCUGUC UGAGCGUUGC UGACCGUGCG GAGCUGCCCC UGGGCUGCAG GCUUCACUGA 180

CAACACCAAG CGUUUUCGAA AGGUCUCACA GAGCACUAUG UACACAAAGG GGUUCAGGCA 240

GCUGUUAGCA UAGCCCAAGC UG 262

<210> 6

<211> 18

<212> DNA

<213> Artificial Sequence

<220>

<223>

<400> 6

CAACAGCTGC CTCAACCC 18

<210> 7

<211> 18

<212> DNA

<213> Artificial Sequence

<220>

<223>

<400> 7

CCTGGTGATC TGCCTCCT 18

<210> 8

<211> 1275

<212> DNA

<213> Human

<400> 8

TAGGTGATGT CAGTGGGAGC CATGAAGAAG GGAGTGGGGA GGGCAGTTGG GCTTGGAGGC 60

GGCAGCGGCT GCCAGGCTAC GGAGGAAGAC CCCCTTCCCA ACTGCGGGGC TTGCGCTCCG 120

GGACAAGGTG GCAGGCGCTG GAGGCTGCCG CAGCCTGCGT GGGTGGAGGG GAGCTCAGCT 180

CGGTTGTGGG AGCAGGCGAC CGGCACTGGC TGGATGGACC TGGAAGCCTC GCTGCTGCCC 240

ACTGGTCCCA ACGCCAGCAA CACCTCTGAT GGCCCCGATA ACCTCACTTC GGCAGGATCA 300

CCTCCTCGCA CGGGGAGCAT CTCCTACATC AACATCATCA TGCCTTCGGT GTTCGGCACC 360

ATCTGCCTCC TGGGCATCAT CGGGAACTCC ACGGTCATCT TCGCGGTCGT GAAGAAGTCC 420

AAGCTGCACT GGTGCAACAA CGTCCCCGAC ATCTTCATCA TCAACCTCTC GGTAGTAGAT 480

CTCCTCTTTC TCCTGGGCAT GCCCTTCATG ATCCACCAGC TCATGGGCAA TGGGGTGTGG 540

CACTTTGGGG AGACCATGTG CACCCTCATC ACGGCCATGG ATGCCAATAG TCAGTTCACC 600

AGCACCTACA TCCTGACCGC CATGGCCATT GACCGCTACC TGGCCACTGT CCACCCCATC 660

TCTTCCACGA AGTTCCGGAA GCCCTCTGTG GCCACCCTGG TGATCTGCCT CCTGTGGGCC 720

CTCTCCTTCA TCAGCATCAC CCCTGTGTGG CTGTATGCCA GACTCATCCC CTTCCCAGGA 780

GGTGCAGTGG GCTGCGGCAT ACGCCTGCCC AACCCAGACA CTGACCTCTA CTGGTTCACC 840

CTGTACCAGT TTTTCCTGGC CTTTGCCCTG CCTTTTGTGG TCATCACAGC CGCATACGTG 900

AGGATCCTGC AGCGCATGAC GTCCTCAGTG GCCCCCGCCT CCCAGCGCAG CATCCGGCTG 960

CGGACAAAGA GGGTGACCCG CACAGCCATC GCCATCTGTC TGGTCTTCTT TGTGTGCTGG 1020

GCACCCTACT ATGTGCTACA GCTGACCCAG TTGTCCATCA GCCGCCCGAC CCTCACCTTT 1080

GTCTACTTAT ACAATGCGGC CATCAGCTTG GGCTATGCCA ACAGCTGCCT CAACCCCTTT 1140

GTGTACATCG TGCTCTGTGA GACGTTCCGC AAACGCTTGG TCCTGTCGGT GAAGCCTGCA 1200

GCCCAGGGGC AGCTTCGCGC TGTCAGCAAC GCTCAGACGG CTGACGAGGA GAGGACAGAA 1260

AGCAAAGGCA CCTGA 1275

<210> 9

<211> 422

<212> PRT

<213> Human

<400> 9

MeT Ser Val Gly Ala MeT Lys Lys Gly Val Gly Arg Ala Val Gly Leu
1 5 10 15

Gly Gly Gly Ser Gly Cys Gln Ala Thr Glu Glu Asp Pro Leu Pro Asn
20 25 30

Cys Gly Ala Cys Ala Pro Gly Gln Gly Gly Arg Arg Trp Arg Leu Pro
35 40 45

Gln Pro Ala Trp Val Glu Gly Ser Ser Ala Arg Leu Trp Glu Gln Ala
50 55 60

Thr Gly Thr Gly Trp MeT Asp Leu Glu Ala Ser Leu Leu Pro Thr Gly
65 70 75 80

Pro Asn Ala Ser Asn Thr Ser Asp Gly Pro Asp Asn Leu Thr Ser Ala
85 90 95

Gly Ser Pro Pro Arg Thr Gly Ser Ile Ser Tyr Ile Asn Ile Ile MeT
100 105 110

Pro Ser Val Phe Gly Thr Ile Cys Leu Leu Gly Ile Ile Gly Asn Ser

115 120 125

Thr Val Ile Phe Ala Val Val Lys Lys Ser Lys Leu His Trp Cys Asn

130 135 140

Asn Val Pro Asp Ile Phe Ile Ile Asn Leu Ser Val Val Asp Leu Leu

145 150 155 160

Phe Leu Leu Gly MeT Pro Phe MeT Ile His Gln Leu MeT Gly Asn Gly

165 170 175

Val Trp His Phe Gly Glu Thr MeT Cys Thr Leu Ile Thr Ala MeT Asp

180 185 190

Ala Asn Ser Gln Phe Thr Ser Thr Tyr Ile Leu Thr Ala MeT Ala Ile

195 200 205

Asp Arg Tyr Leu Ala Thr Val His Pro Ile Ser Ser Thr Lys Phe Arg

210 215 220

Lys Pro Ser Val Ala Thr Leu Val Ile Cys Leu Leu Trp Ala Leu Ser

225 230 235 240

Phe Ile Ser Ile Thr Pro Val Trp Leu Tyr Ala Arg Leu Ile Pro Phe

245 250 255

Pro Gly Gly Ala Val Gly Cys Gly Ile Arg Leu Pro Asn Pro Asp Thr

260 265 270

Asp Leu Tyr Trp Phe Thr Leu Tyr Gln Phe Phe Leu Ala Phe Ala Leu

275 280 285

Pro Phe Val Val Ile Thr Ala Ala Tyr Val Arg Ile Leu Gln Arg MeT

290 295 300

Thr Ser Ser Val Ala Pro Ala Ser Gln Arg Ser Ile Arg Leu Arg Thr

305 310 315 320

Lys Arg Val Thr Arg Thr Ala Ile Ala Ile Cys Leu Val Phe Phe Val

325 330 335

Cys Trp Ala Pro Tyr Tyr Val Leu Gln Leu Thr Gln Leu Ser Ile Ser

340 345 350

Arg Pro Thr Leu Thr Phe Val Tyr Leu Tyr Asn Ala Ala Ile Ser Leu
355 360 365

Gly Tyr Ala Asn Ser Cys Leu Asn Pro Phe Val Tyr Ile Val Leu Cys
370 375 380

Glu Thr Phe Arg Lys Arg Leu Val Leu Ser Val Lys Pro Ala Ala Gln
385 390 395 400

Gly Gln Leu Arg Ala Val Ser Asn Ala Gln Thr Ala Asp Glu Glu Arg
405 410 415

Thr Glu Ser Lys Gly Thr
420

<210> 10

<211> 31

<212> DNA

<213> Artificial Sequence

<220>

<223>

<400> 10

GTCGACATGG ACCTGGAAGC CTCGCTGCTG C 31

<210> 11

<211> 31

<212> DNA

<213> Artificial Sequence

<220>

<223>

<400> 11

ACTAGTTCAG GTGCCTTTGC TTTCTGTCCT C 31

<210> 12

<211> 33

<212> DNA

<213> Artificial Sequence

<220>

<223>

<400> 12

AGTCGACATG TCAGTGGGAG CCATGAAGAA GGG 33

<210> 13

<211> 33

<212> DNA

<213> Artificial Sequence

<220>

<223>

<400> 13

AACTAGTTCA GGTGCCTTTG CTTTCTGTCC TCT 33

<210> 14

<211> 1074

<212> DNA

<213> Human

<400> 14

GTCGACATGG ACCTGGAAGC CTCGCTGCTG CCCACTGGTC CCAACGCCAG CAACACCTCT 60

GATGGCCCCG ATAACCTCAC TTCGGCAGGA TCACCTCCTC GCACGGGGAG CATCTCCTAC 120

ATCAACATCA TCATGCCTTC GGTGTTCGGC ACCATCTGCC TCCTGGGCAT CATCGGGAAC 180

TCCACGGTCA TCTTCGCGGT CGTGAAGAAG TCCAAGCTGC ACTGGTGCAA CAACGTCCCC 240

GACATCTTCA TCATCAACCT CTCGGTAGTA GATCTCCTCT TTCTCCTGGG CATGCCCTTC 300

ATGATCCACC AGCTCATGGG CAATGGGGTG TGGCACTTTG GGGAGACCAT GTGCACCCTC 360

ATCACGGCCA TGGATGCCAA TAGTCAGTTC ACCAGCACCT ACATCCTGAC CGCCATGGCC 420

ATTGACCGCT ACCTGGCCAC TGTCCACCCC ATCTCTTCCA CGAAGTTCCG GAAGCCCTCT 480

GTGGCCACCC TGGTGATCTG CCTCCTGTGG GCCCTCTCCT TCATCAGCAT CACCCCTGTG 540

TGGCTGTATG CCAGACTCAT CCCCTTCCCA GGAGGTGCAG TGGGCTGCGG CATACGCCTG 600

CCCAACCCAG ACACTGACCT CTACTGGTTC ACCCTGTACC AGTTTTTCCT GGCCTTTGCC 660

CTGCCTTTTG TGGTCATCAC AGCCGCATAC GTGAGGATCC TGCAGCGCAT GACGTCCTCA 720

GTGGCCCCCG CCTCCCAGCG CAGCATCCGG CTGCGGACAA AGAGGGTGAC CCGCACAGCC 780

ATCGCCATCT GTCTGGTCTT CTTTGTGTGC TGGGCACCCT ACTATGTGCT ACAGCTGACC 840

CAGTTGTCCA TCAGCCGCCC GACCCTCACC TTTGTCTACT TATACAATGC GGCCATCAGC 900

TTGGGCTATG CCAACAGCTG CCTCAACCCC TTTGTGTACA TCGTGCTCTG TGAGACGTTC 960

CGCAAACGCT TGGTCCTGTC GGTGAAGCCT GCAGCCCAGG GGCAGCTTCG CGCTGTCAGC 1020

AACGCTCAGA CGGCTGACGA GGAGAGGACA GAAAGCAAAG GCACCTGAAC TAGT 1074

<210> 15

<211> 1283

<212> DNA

<213> Human

<400> 15

AGTCGACATG TCAGTGGGAG CCATGAAGAA GGGAGTGGGG AGGGCAGTTG GGCTTGGAGG 60

CGGCAGCGGC TGCCAGGCTA CGGAGGAAGA CCCCCTTCCC AACTGCGGGG CTTGCGCTCC 120

GGGACAAGGT GGCAGGCGCT GGAGGCTGCC GCAGCCTGCG TGGGTGGAGG GGAGCTCAGC 180

TCGGTTGTGG GAGCAGGCGA CCGGCACTGG CTGGATGGAC CTGGAAGCCT CGCTGCTGCC 240

CACTGGTCCC AACGCCAGCA ACACCTCTGA TGGCCCCGAT AACCTCACTT CGGCAGGATC 300

ACCTCCTCGC ACGGGGAGCA TCTCCTACAT CAACATCATC ATGCCTTCGG TGTTCGGCAC 360

CATCTGCCTC CTGGGCATCA TCGGGAACTC CACGGTCATC TTCGCGGTCG TGAAGAAGTC 420

CAAGCTGCAC TGGTGCAACA ACGTCCCCGA CATCTTCATC ATCAACCTCT CGGTAGTAGA 480

TCTCCTCTTT CTCCTGGGCA TGCCCTTCAT GATCCACCAG CTCATGGGCA ATGGGGTGTG 540

GCACTTTGGG GAGACCATGT GCACCCTCAT CACGGCCATG GATGCCAATA GTCAGTTCAC 600

CAGCACCTAC ATCCTGACCG CCATGGCCAT TGACCGCTAC CTGGCCACTG TCCACCCCAT 660

CTCTTCCACG AAGTTCCGGA AGCCCTCTGT GGCCACCCTG GTGATCTGCC TCCTGTGGGC 720

CCTCTCCTTC ATCAGCATCA CCCCTGTGTG GCTGTATGCC AGACTCATCC CCTTCCCAGG 780

AGGTGCAGTG GGCTGCGGCA TACGCCTGCC CAACCCAGAC ACTGACCTCT ACTGGTTCAC 840

CCTGTACCAG TTTTTCCTGG CCTTTGCCCT GCCTTTTGTG GTCATCACAG CCGCATACGT 900

GAGGATCCTG CAGCGCATGA CGTCCTCAGT GGCCCCCGCC TCCCAGCGCA GCATCCGGCT 960

GCGGACAAAG AGGGTGACCC GCACAGCCAT CGCCATCTGT CTGGTCTTCT TTGTGTGCTG 1020

GGCACCCTAC TATGTGCTAC AGCTGACCCA GTTGTCCATC AGCCGCCCGA CCCTCACCTT 1080

TGTCTACTTA TACAATGCGG CCATCAGCTT GGGCTATGCC AACAGCTGCC TCAACCCCTT 1140

TGTGTACATC GTGCTCTGTG AGACGTTCCG CAAACGCTTG GTCCTGTCGG TGAAGCCTGC 1200

AGCCCAGGGG CAGCTTCGCG CTGTCAGCAA CGCTCAGACG GCTGACGAGG AGAGGACAGA 1260

AAGCAAAGGC ACCTGAACTA GTT 1283

〈210〉 16

〈211〉 420

〈212〉 RNA

〈213〉 Human

〈400〉 16

CAAAAGCUGG AGCUCCACCG CGGUGGCGGC CGCUCUAGCC CACUAGUUCA GGUGCCUUUG 60

CUUUCUGUCC UCUCCUCGUC AGCCGUCUGA GCGUUGCUGA CAGCGCGAAG CUGCCCCUGG 120

GCUGCAGGCU UCACCGACAG GACCAAGCGU UUGCGGAACG UCUCACAGAG CACGAUGUAC 180

ACAAAGGGGU UGAGGCAGCU GUUGGCAUAG CCCAAGCUGA UGGCCGCAUU GUAUAAGUAG 240

ACAAAGGUGA GGGUCGGGCG GCUGAUGGAC AACUGGGUCA GCUGUAGCAC AUAGUAGGGU 300

GCCCAGCACA CAAAGAAGAC CAGACAGAUG GCGAUGGCUG UGCGGGUCAC CCUCUUUGUC 360

CGCAGCCGGA UGCUGCGCUG GGAGGCGGGG GCCACUGAGG ACGUCAUGCG CUGCAGGAUC 420